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(71) Applicant *(for all designated States except US)*: PHARMACIA + UPJOHN COMPANY [US/US]; 301 Henrietta Street, Kalamazoo, MI 49001 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: HUTCHINSON, Douglas, K. [US/US]; Apartment 613, 109 East Candlewyck, Kalamazoo, MI 49001 (US).

(74) Agent: CORNEGLIO, Donald, L.; Pharmacia + Upjohn Company, Corporate Intellectual Property Law, 301 Henrietta Street, Kalamazoo, MI 49001 (US).

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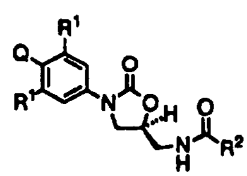
(54) Title: HETERO-AROMATIC RING SUBSTITUTED PHENYLOXAZOLIDINONE ANTIMICROBIALS

(57) Abstract

A hetero-aromatic (Q) substituted phenyloxazolidinone antimicrobial of Formula (I) wherein Q is a 5-member hetero-aromatic having from one to four nitrogen atoms or alternatively a benzoannulated 5-member hetero-aromatic having from one to four nitrogen atoms where R^1 is independently H, OCH_3, F, or Cl; R^2 is hydrogen, C_1-C_8 alkyl (optionally substituted with one or more of F, Cl, hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy), C_3-C_6 cycloalkyl, amino, C_1-C_8 alkylamino, C_1-C_8 dialkylamino, C_1-C_8 alkoxy; and each Q is optionally substituted with one or more of H, F, Cl, Br, OR^4, SR^4, $S(O)_nR^4$ (n = 1 or 2), CN, O_2CR^4, $NHCOR^4$, $NHCO_2R^4$, $NHSO_2R^4$, CO_2R^4, $CON(R^4)_2$, COR^4, C_1-C_8 straight or branched chain alkyl or C_3-C_8 cycloalkyl, optionally substituted with one or more of (a)-(m), or Phenyl, optionally substituted with one or more of the preceeding groups listed under (a)-(n); and R^4 is H, C_1-C_6 straight or branched chain alkyl or C_3-C_8 cycloalkyl, optionally substituted with one or more of fluorine, chlorine, hydroxy, C_1-C_4 alkoxy, C_1-C_4 acyl, C_1-C_4 acyloxy, or $O_2CCH_2N(CH_3)_2$, or Phenyl, optionally substituted with one or more of fluorine, chlorine, C_1-C_4 straight or branched chain alkyl, hydroxy, C_1-C_4 alkoxy, C_1-C_4 acyl, C_1-C_4 acyloxy, or $O_2CCH_2N(CH_3)_2$.



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HETERO-AROMATIC RING SUBSTITUTED PHENYLOXAZOLIDINONE ANTIMICROBIALS

Background of the Invention

The subject invention discloses new and useful phenyloxazolidinone compounds having a nitrogen containing hetero-aromatic ring substitution attached through one of the nitrogen atoms. More particularly a 5-member nitrogen containing aromatic ring having from 1 to 4 nitrogen atoms one of which binds to the phenyloxazolidinone. The compounds are useful antimicrobial agents, effective against a number of human and veterinary pathogens, including gram-positive aerobic bacteria such as multiply-resistant staphylococci, streptococci and enterococci as well as anaerobic organisms such as *Bacteroides spp.* and *Clostridia spp.* species, and acid-fast organisms such as *Mycobacterium tuberculosis*, *Mycobacterium avium* and *Mycobacterium spp.*.

Information Disclosure

The present compounds are related by their phenyloxazolidinone ring structure to the compounds disclosed in the publications below except that the subject compounds have a nitrogen containing hetero-aromatic ring substitution attached to the phenyloxazolidinone by one of the nitrogen atoms. This attachment point facilitates a different but easier synthesis than a corresponding carbon-carbon bond structure and therefore presents an advantage over such compounds. The instant compounds are unique and have useful antibacterial activity.

PCT/US93/03570 application discloses oxazolidinones containing a substituted diazine moiety and their uses as antimicrobials.

PCT/US92/08267 application discloses substituted aryl and heteroaryl-phenyl-oxazolidinones useful as antibacterial agents. In one aspect, it discloses 5-member nitrogen hetero-aromatic rings attached to a phenyloxazolidinone although there is no synthesis disclosed which would permit attachment through the nitrogen atom (see, Chart C (v, w, ee and ff)).

PCT/US89/03548 application discloses 5'indolinyl-5ß-amidomethyloxazolidinones, 3-(fused-ring substituted)phenyl-5ß-amidomethyloxazolidinones, and 3-(nitrogen substituted)phenyl-5ß-amidomethyloxazolidinones which are useful as antibacterial agents.

Other references disclosing various oxazolidinones include US Patent 4,801,600, 4,921,869, Gregory W. A., et al., J. Med. Chem., 32, 1673-81 (1989);

Gregory W. A., et al., J. Med. Chem., 33, 2569-78 (1990); Wang C., et al., Tetrahedron, 45, 1323-26 (1989); and Brittelli, et al., J. Med. Chem., 35, 1156 (1992).

European Patent Publication 352,781 discloses phenyl and pyridyl substituted phenyl oxazolidinones.

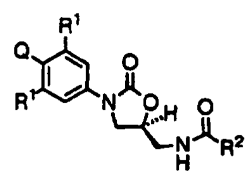
European Patent Publication 316,594 discloses 3-substituted styryl oxazolidinones.

European Patent Publication 312,000 discloses phenylmethyl and pyridinylmethyl substituted phenyl oxazolidinones.

U.S. 5,254,577 discloses nitrogen hetero-aromatic rings attached to phenyloxazolidinone but not by the hetero-aromatic nitrogen (see, Col. 19 and 43).

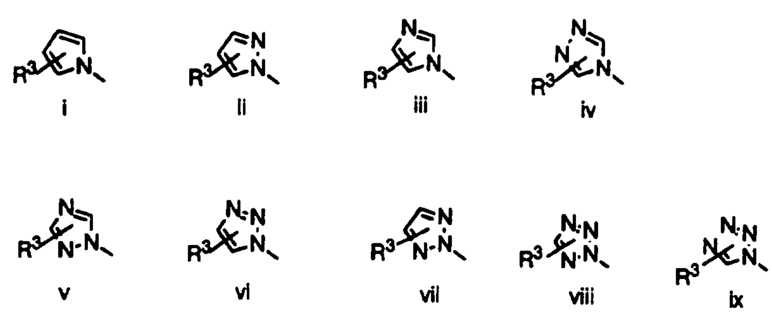
Summary of the Invention:

In one aspect the subject invention is a compound of structural Formula I:

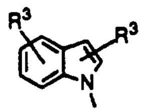


or pharmaceutically acceptable salts thereof wherein:

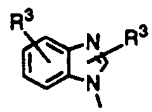
Q is a hetero-aromatic 5-member ring bound to the aromatic ring of I at the nitrogen of the structures i, ii, iii, iv, v, vi, vii, viii, or ix:



or alternatively Q can be a benzoannulated hetero-aromatic 5-member ring bound to the aromatic ring of I at the nitrogen of the structures x, xi, xii, xiii, xiv, xv, xvi or xviii:



x



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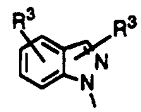
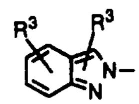


xii



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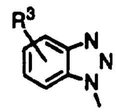

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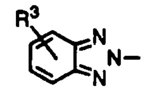
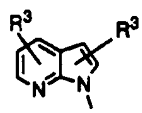
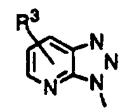


xv



xvi



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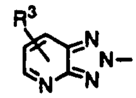


xviii

R^1 is independentlyl H, OCH_3, F, or Cl;

R^2 is (a) hydrogen,

(b) C_1-C_8 alkyl optionally substituted with one or more of the following: F, Cl, hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy;

(c) C_3-C_6 cycloalkyl;

(d) amino;

(e) C_1-C_8 alkylamino;

(f) C_1-C_8 dialkylamino;

(g) C_1-C_8 alkoxy;

R^3 is each independently selected from

(a) H,

(b) F, Cl, Br,

(c) OR^4,

(d) SR^4,

(e) $S(O)_nR^4$ (n is 1 or 2),

(f) CN,

(g) O_2CR^4,

(h) $NHCOR^4$,

(i) $NHCO_2R^4$,

(j) $NHSO_2R^4$,

(k) CO_2R^4,

(l) $CON(R^4)_2$,

(m) COR^4,

(n) C_1-C_8 straight or branched chain alkyl or C_3-C_8 cycloalkyl, optionally substituted with one or more of (a)-(m), or

(o) Phenyl, optionally substituted with one or more of the preceeding groups listed under (a)-(n); and

R^4 is

(a) H,

(b) C_1-C_6 straight or branched chain alkyl or C_3-C_8 cycloalkyl, optionally substituted with one or more of fluorine, chlorine, hydroxy, C_1-C_4 alkoxy, C_1-C_4 acyl, C_1-C_4 acyloxy, or $O_2CCH_2N(CH_3)_2$, or

(c) Phenyl, optionally substituted with one or more of fluorine, chlorine, C_1-C_4 straight or branched chain alkyl, hydroxy, C_1-C_4 alkoxy, C_1-C_4 acyl, C_1-C_4 acyloxy, or $O_2CCH_2N(CH_3)_2$.

Detailed Description of the Invention

The present invention discloses novel substituted 5-member nitrogen heterocyclic phenyloxazolidinones according to structural Formula I above.

"Alkyl" means carbon atom chains having the designated number of carbon atoms which can be either straight chained or branched.

"Alkoxy" means the designated number of carbon atoms attached to an oxygen forming such groups as methoxy ($-OCH_3$), ethyloxy, butyloxy, etc. and isomeric forms thereof.

"Acyloxy" means the designated number of carbon atoms to form an organic acid where the OH group has been deleted, such as acetyl, CH_3 CO-; benzoyl, C_6 H_5CO-.

Cycloalkyl" means the designated number of carbon atoms forming cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. and isomeric forms thereof.

"Amino" means an NH_2, "alkylamino" is where one of the hydrogen positions is replaced by an alkyl and "dialkylamino" is where both hydrogens are replaced by an alkyl group.

"Pharmaceutically acceptable salts" are acid addition salts which can be prepared by any of the art recognized means. Typical, acid addition salts include hydrochloride, hydrobromide, hydroiodide, sulfate, phosphate, acetate, propionate, lactate, malate, succinate, tartrate, cyclohexanesulfamates, methanesulfonates,

ethanesulfonates, benxenesulfonates, toluenesulfonates, fumarates and other pharmaceutically acceptable couter ions for amines.

The compounds are useful as antimicrobial agents, effective against a number of human and veterinary pathogens, particularly aerobic Gram-positive bacteria, including multiply-antibiotic resistant staphylococci and streptococci, as well as anaerobic organisms such as bacteroides and clostridia species, and acid-fast organisms such as *Mycobacterium tuberculosis* and other mycobacterium species.

The pharmaceutical compositions of this invention may be prepared by combining the compounds of Formula I of this invention with a solid or liquid pharmaceutically acceptable carrier and, optionally, with pharmaceutically acceptable adjuvants and excipients employing standard and conventional techniques. Solid form compositions include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be at least one substance which may also function as a diluent, flavoring agent, solubilizer, lubricant, suspending agent, binder, tablet disintegrating agent, and encapsulating agent. Inert solid carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, cellulosic materials, low melting wax, cocoa butter, and the like. Liquid form compositions include solutions, suspensions and emulsions. For example, there may be provided solutions of the compounds of this invention dissolved in water and water-propylene glycol and water-polyethylene glycol systems, optionally containing suitable conventional coloring agents, flavoring agents, stabilizers and thickening agents.

Preferably, the pharmaceutical composition is provided employing conventional techniques in unit dosage form containing effective or appropriate amounts of the active component, that is, the compound of Formula I according to this invention.

The quantity of active component, that is the compound of Formula I according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application, the potency of the particular compound, the desired concentration. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

In therapeutic use for treating, or combatting, bacterial infections in warm-blooded animals, patients suffering from an antimicrobial infection, the compounds or pharmaceutical compositions thereof will be administered orally and/or parenterally at a dosage to obtain and maintain a concentration, that is, an amount,

or blood-level of active component in the animal undergoing treatment which will be antibacterially effective. Generally, such antibacterially effective amount of dosage of active component will be in the range of about 0.1 to about 100, more preferably about 3.0 to about 50 mg/kg of body weight/day. It is to be understood that the dosages may vary depending upon the requirements of the patient, the severity of the bacterial infection being treated, and the particular compound being used. Also, it is to be understood that the initial dosage administered may be increased beyond the above upper level in order to rapidly achieve the desired blood-level or the initial dosage may be smaller than the optimum and the daily dosage may be progressively increased during the course of treatment depending on the particular situation. If desired, the daily dose may also be divided into multiple doses for administration, e.g., two to four times per day.

The compounds of Formula I according to this invention are administered parenterally, i.e., by injection, for example, by intravenous injection or by other parenteral routes of administration. Pharmaceutical compositions for parenteral administration will generally contain a pharmaceutically acceptable amount of the compound according to Formula I as a soluble salt (acid addition salt or base salt) dissolved in a pharmaceutically acceptable liquid carrier such as, for example, water-for-injection and a buffer to provide a suitably buffered isotonic solution, for example, having a pH of about 3.5-6. Suitable buffering agents include, for example, trisodium orthophosphate, sodium bicarbonate, sodium citrate, N-methylglucamine, L(+)-lysine and L(+)-arginine to name but a few representative buffering agents. The compound according to Formula I generally will be dissolved in the carrier in an amount sufficient to provide a pharmaceutically acceptable injectable concentration in the range of about 1 mg/ml to about 400 mg/ml of solution. The resulting liquid pharmaceutical composition will be administered so as to obtain the above-mentioned antibacterially effective amount of dosage. The compounds of Formula I according to this invention are advantageously administered orally in solid and liquid dosage forms.

The most preferred compounds in this series would be prepared as the optically pure enantiomers having the (S)- configuration according to the Cahn-Ingold-Prelog notation at C5 of the oxazolidinone ring. Optically pure material could be prepared by one of a number of asymmetric syntheses or by resolution from a racemic modification by selective crystallization of a salt from, for example, the racemic modification of intermediate amine **10** (as described in Chart II) with an appropriate optically active acid such as dibenzoyl tartarate or 10-camphorsulfonic

acid, followed by treatment with base to afford the optically active amine. Although the (S)- enantiomer of this series of compounds is preferred since it is pharmacologically active as an antibacterial agent, the racemic modification is also useful in the same manner as the pure (S)- enantiomer: the difference being that twice as much racemic material is required to elicit the same antibacterial effect. In addition, it will be apparent to those skilled in the art that when a chiral center exists in any of the substituents bonded to Q that diastereomers are possible. These diastereomers, either in the racemic or configurationally enriched forms, are within the scope of compounds of structural Formula I of this invention.

The preferred method of preparation of compounds of structural Formula I in highly enantiomerically enriched form is depicted in Charts I-VIII.

As shown in Chart I, 5-ring heterocyclics of general structure **1**(where n = number of nitrogen atoms in the ring), available either commercially or by syntheses described in the literature (see for example, Katritzky, *et al.* in "Comprehensive Heterocyclic Chemistry") are treated with a substituted nitrobenzene derivative **2**(Y is halogen or trifluoromethanesulfonyloxy) in a suitable base and solvent combination, for example potassium carbonate in DMSO, at a suitable temperature, typically ambient to 90°C, to afford adduct **3**. This method works well for 5-ring heterocyclics such as imidazole, pyazole, and the like. For 5-ring heterocyclics **1**, such as pyrrole or indole and the like, the heterocyclic is added to a suspension of a strong base such as sodium hydride, potassium *tert*-butoxide, or the like in THF or DME or similar solvents to form the alkalai metal salt **4**, which is then treated with nitroaromatic **2** at temperatures in the range of 0°C to the reflux temperature of the solvent to afford adduct **3**. The nitro derivative **3** is then reduced by catalytic hydrogenation in the presence of a suitable catalyst, such as palladium on carbon, W-2 Raney nickel or platinum on sulfide carbon, in a suitable solvent, such as ethyl acetate, THF, methanol or combinations therof, to afford the aniline derivative **5**. When THF is used as solvent for this reduction, it is not necessary to remove the catalyst by filtration or to isolate aniline derivative **5**, but merely to purge the reaction vessel with an inert gas such as nitrogen and add saturated sodium bicarbonate solution and treat the resulting cooled reaction mixture with either benzyl or methyl chloroformate to give the corresponding benzyl (R is CH_2Ph) or methyl carbamate (R is CH_3) derivatives **6**.

Either of the carbamate derivatives **6** can be deprotonated with a lithium base such as n-butyllithium, lithium diisopropylamide (LDA), or lithium bis(trimethylsilyl)amide (LHMDS) in a suitable solvent such as THF,

N,N-dimethylformamide (DMF), or mixtures thereof, at a suitable temperature, typically -78°C to -40°C to give a lithiated intermediate which is directly treated with (R)-(-)-glycidyl butyrate. Warming this reaction mixture to ambient or higher temperatures then affords the (hydroxymethyl)oxazolidinone **7** in highly enantiomerically enriched form.

Chart II describes the conversion of (hydroxymethyl)oxazoldinone **7** into oxazoldinone antibacterial agents of Structural Formula I. As shown, compound **7** can be converted into the corresponding mesylate (R = CH_3) or tosylate (R = p-$CH_3C_6H_4$) by treatment with methanesulfonyl chloride in the presence of triethylamine or pyridine or p-toluenesulfonyl chloride in the presence of pyridine, respectively. The resulting sulfonate **8** can be treated with an alkalai metal azide, such as sodium or potassium azide in an aprotic dipolar solvent such as DMF or N-methylpyrrolidinone (NMP) with an optional catalyst such as 18-crown-6 at a temperature in the range of 50-90°C to afford azide **9**. The azide **9** can be reduced to the corresponding amine **10** by hydrogenation in the presence of a palladium, platinum or nickel catalyst, in an appropriate solvent such as ethyl acetate, THF, or methanol. Alternatively, azide **9** can be reduced to amine **10** by treatment with triphenylphosphine or other trivalent phosphorus compounds in a solvent such as THF, followed by addition of water. Amine **10** can also be prepared by treatment of the sulfonate **8** with potassium phthalimidate in DMF at 40-60°C or in refluxing acetonitrile to afford the phthalimide **11**, which is deprotected by treatment, for example, with aqueous methylamine in refluxing ethanol. A more direct route to amine **10** is to treat sulfonate **8** with aqueous ammonia solution in an isopropyl alcohol-THF solvent system in a sealed tube heated at 75-105°C in an oil bath. Amine **10** is then acylated by reactions well-known to those skilled in the art to give (acylaminomethyl)oxazoldinones of structural formula **12**. For example, amine **10** can be treated with an acid chloride or anhydride in the presence of a base such as pyridine or triethylamine at temperatures ranging from -40-40°C to provide the acyl derivative **12**. It can also be seen that other acyl derivatives, such as carbamates, can be prepared under similar reaction conditions. It can easily be seen that preparation of **12** provides an example of compounds of Structural Formula I. It can also be seen that in some cases, **12** can be transformed into other compounds of Structural Formula I by treatment with 40% aqueous formaldehyde in dimethyl sulfoxide at temperatures in the range of 90-150°C optionally in the presence of an acid catalyst to afford the corresponding hydroxymethyl derivative **13**.

Alternatively, compound **13** can be prepared by a less direct route, which offers the potential of providing other regioisomers that cannot be readily obtained by hydroxymethylation. As shown in Chart III, alkoxycarbonyl derivatives of 5-membered ring heterocycles, **14**(where m = number of methylenes), either available commercially or prepared by literature methods, can be treated with a nitrobenzene derivative **2** in a suitable solvent, such as DMSO, DMF, or the like, in the presence of a suitable base such as potassium carbonate at a suitable temperature in the range ambient to 90°C to afford the biaryl derivative **15**. The resulting nitro derivative is then reduced by catalytic hydrogenation in the presence of a suitable catalyst, such as palladium on carbon, W-2 Raney nickel, or platinum on sulfide carbon, in a suitable solvent, such as ethyl acetate, THF, methanol, or combinations thereof, to afford aniline derivative **16**. When THF is used as solvent for this reduction, it is not necessary to remove the catalyst by filtration or to isolate aniline derivative **16**, but merely to purge the reaction vessel with an inert gas such as nitrogen and add saturated sodium bicarbonate solution and treat the corresponding mixture with with either benzyl or methyl chloroformate for give the corresponding benzyl (R = CH_2Ph) or methyl (R = CH_3) carbamate derivatives **17**. The ester group of either of the carbamate derivatives **17** can be reduced with either lithium borohydride or possibly with borane-THF complex to afford the corresponding alcohol **18**. It can be seen by those skilled in the art that subsequent transformations of **18** will necessitate the protection of the hydroxyl group. This can be accomplished, for example, by preparation of the *tert*-butyldimethyl silyl (TBS) ether **19**(R = $Si(CH_3)_2t$-Bu) by treatment of **18** with *tert*-butyldimethylchlorosilane in the presence of a base such as imidazole or diisopropylethylamine, optionally in the presence of 4-dimethylaminopyridine as a catalyst, in a suitable solvent such as DMF, THF, or dichloromethane. Either of the carbamate derivatives **19** can be deprotonated with a lithium base such as lithium diisopropylamide (LDA) or lithium bis(trimethylsilyl)amide (LHMDS), in a suitable solvent such as THF, DMF or mixtures therof, at a suitable temperature, typically -78°C to -40°C to give a lithiated intermediate which is directly treated with (R)-(-)-glycidiyl butyrate. Warming this reaction mixture to ambient or higher temperatures then affords the (hydroxymethyl)oxazoldinone **20** in highly enantiomerically enriched form.

Chart IV describes the conversion of (hydroxymethyl)oxazolidinone **20** into oxazolidinone antibacterial agents of Structural Formula I. As shown, compound **20** can be converted to the corresponding (acylaminomethyl)oxazoldinone **21**(R =

straight or branched chain alkyl) by a sequence of reactions identical with that used to convert **7** to **12** in Chart II. (Acylaminomethyl)oxazolidinone **21** can then be deprotected by a number of methods, notably by treatment with methanolic HCl solution at reflux or by treatment with mixtures of acetic acid in THF-water at temperatures of 40-90°C to afford alcohol **22**. Alcohol **22** is an example of an oxazolidinone antibacterial agent of Structural Formula I. Further transformations outlined in Chart IV can be used to prepare other compounds of Structural Formula I from compound **22**. As shown, alcohol **22** can be oxidized by treatment with reagents such as pyridinium dichromate in DMF or by treatment with oxgen gas in the presence of a noble metal catalyst in water solution or other methods known to thoses skilled in the art, to afford carboxylic acid **23**. Carboxylic acid **23** can be esterified by treatment with an appropriate alkyl halide in the presence of a base such as potassium carbonate in an appropriate solvent, such as acetone, to give ester **24**(R = straight or branched chain alkyl). Alternatively, ester **24** can be obtained by addition of carboxylic acid **23** to a solution of gaseous HCl dissolved in an appropriate alcohol, or by other means known to those skilled in the art.

Chart V outlines methods by which alcohol **22** can be converted into other compounds of Structural Formula I. As shown, **22** can be converted into the corresponding mesylate (R = CH_3) or tosylate (R = p-$CH_3C_6H_4$) by treatment with methanesulfonyl chloride in the presence of triethylamine or pyridine or with p-toluenesulfonyl chloride in the presence of pyridine. The resulting sulfonate derivative **25** can be treated with an alkalai metal salt of a mercaptan (R = straight or branched chain alkyl or aryl) in an aprotic dipolar solvent such as DMF, DMSO, or acetonitrile with an optional catalyst such as 18-crown-6 at a temperature in the range of ambient to 90°C to afford sulfide **26**. Sulfide **26** can then be further transformed into either sulfoxide **27** or sulfone **28** by oxidation with appropriate stoichiometric amounts of a suitable oxidizing agent, such as m-chloroperoxybenzoic acid (MCPBA) in a suitable solvent such as dichloromethane, diethyl ether, or the like. Alternatively, sulfone **28** could be obtained directly by treatment with osmium tetroxide or ruthenium tetroxide in the presence of sodium periodate or by treatment with potassium hydrogen persulfate. Compounds **26**, **27**, and **28** constitute examples of compounds of Structural Formula I .

Other possible transformations of alcohol **22** are shown in Chart V. As shown, sulfonate derivative **25** can be treated with an alkalai metal azide in a dipolar aprotic solvent such as DMF, DMSO, acetonitrile or the like, optionally in

the presence of a catalyst such as 18-crown-6, at a temperature in the range of 50-90°C to afford azide **29**. The azide **29** can then be reduced to the corresponding amine **30** by hydrogenation in the presence of a platinum , palladium, or nickel catalyst, in an appropriate solvent such as ethyl acetate, THF or methanol. Alternatively, azide **29** can be reduced by treatment with triphenylphoshine or other trivalent phosphorus compounds in a solvent such as THF, followed by addition of water. Amine **30** can then be used to form the corresponding sufonamide derivative **31** by treatment with an appropriate sulfonyl chloride (R = straight or branched chain alkyl, or aryl) in an appropriate solvent, such as pyridine. It can be seen that sulfonamide derivative **31** is an example of compounds of Structural Formula I.

Due to the shortage of commercially available 3-substituted heterocyclics in the pyrrole, pyrazole, or triazole series, some of the possible compounds of Structural formula I cannot be readily prepared by routes described in the previous Charts. As a result, the synthesis of these other heterocyclic oxazolidinone derivatives from aniline derivative **37** are described in Charts VI, VII, VIII, and IX.

The preparation of aniline derivative **37** is described in Chart VI. As shown, nitroaromatic **2** is treated with benzylamine in the presence of a suitable base, such as triethylamine or N,N-diisopropylethylamine, in a solvent such as acetonitrile, to afford displacement product **32**. Nitro compound **32** can then be transformed into optically active oxazoldinone derivative **36** by methods used in Charts I and II to convert nitro derivative **3** into oxazolidinone **12**. At this point in the synthesis, hydrogenolysis of **36** using palladium on carbon as catalyst and methanol as solvent serves to both remove the CbZ protecting group and the benzyl protecting group to give aniline **37**.

Preparation of 3-substituted pyrrole derivatives can be accomplished as shown in Chart VI. Treatment of aniline **37** with the commercially available 3.5-dimethoxy-3-tetrahydrofurancarboxaldehyde under conditions of acid catalysis, such as in refluxing acetic acid, to afford 3-pyrrolecarboxaldehyde **38**. Aldehyde **38** can then be transformed into other pyrrole analogs, such as hydroxymethyl pyrrole **39**, ester **40**, or oxime derivative **41** by methods well-known to those skilled in the art. It can be seen that pyrroles **30**, **40** and **41** constitute examples of compounds of structural Formula I.

Transformation of aniline **37** into substituted triazole derivatives is described in Chart VII. As shown, diazotization of aniline **37** by treatment with nitrous acid, followed by addition of sodium azide, allows formation of azide **42** which is a useful

precursor to formation of triazoles by means of a 1,3-dipolar cycloaddition with a substituted acetylene, **43**. As shown, treatment of azide **42** with a substituted acetylene derivative **43** in a solvent such as benzene, toluene, and the like, at temperatures in the range of ambient to 120°C, optionally in the presence of a Lewis acid catalyst such as aluminum chloride, boron trifluoride etherate, titanium tetrachloride, or the like, affords the substituted triazole derivative **44**. Alternatively, in the case where one of the R^3 groups of **43** is an acyl group, such as R^4CO in acetylene **45**, the cycloaddition under the aforementioned conditions will give preferentially the 4-acyl triazole derivative **46** with lesser amounts of the corresponding 5-acyl triazole derivative **47**. Alternatively, functionality permissible in R^3 of **44** can be used to transform **44** into acyl derivatives **46** and/or **47**. 4-Acyl triazole oxazolidinone **46** can be transformed into oxime derivatives **48** or hydroxy compound **49** by methods known to those skilled in the art. It can be seen that **46**, **48** and **49** constitute examples of compounds of structural Formula I.

Transformation of aniline **37** into both possible regioisomers of substituted pyrazole derivatives is shown in chart VIII. As shown, diazotization of aniline **37** followed by reduction of the diazonium salt with either tin [II] chloride or in-situ generated sodium sulfite gives the hyrazine derivative **50**. It can be seen that hydrazine **50** can be reacted with triformylmethane, **51** (*Synthesis* **1989**, 858), to form the pyrazole-4-carboxaldehyde **52**, as shown. Alternatively, treatment of hydrazine **50** with 4-methoxy-2-oxo-but-3-enoic acid, ethyl ester, **53** (*Helv. Chim. Acta* **1967**, *50*, 128), will lead to the formation of the regioisomeric 3-carboethoxypyrazole **54**. It can be seen that aldehyde **52** and ester **54** can be converted into other series of analogs by transformations described in Charts IV, V, and VI. It can be seen that **52** and **54** constitute examples of compounds of structural Formula I.

Examples of heteroaryl-phenyloxazolidinones which can be prepared as part of this invention are as follows:

(S)-N-[[3-[3-Fluoro-4-(1H-pyrrol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(3-carbomethoxy-1H-pyrrol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(1H-pyrrol-1-yl-3-carboxaldehyde)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(3-(hydroxyiminomethyl)-1H-pyrrol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(3-(methoxyiminomethyl)-1H-pyrrol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(S)-N-[[3-[3-Fluoro-4-(3-hydroxymethyl-1H-pyrrol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(S)-N-[[3-[3-Fluoro-4-[3-(2-carboethoxyvinyl)-1H-pyrrol-1-yl]phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide;
(S)-N-[[3-[3-Fluoro-4-[3-(2-carboethoxyethyl)-1H-pyrrol-1-yl]phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide;
(S)-N-[[3-[3-Fluoro-4-[3-(3-hydroxypropyl)-1H-pyrrol-1-yl]phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide;
(S)-N-[[3-[3-Fluoro-4-[3-(3-methanesulfonylaminopropyl)-1H-pyrrol-1-yl]phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide;
(S)-N-[[3-[3-Fluoro-4-(1H-imidazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(S)-N-[[3-[3-Fluoro-4-(4-methyl-1H-imidazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(S)-N-[[3-[3-Fluoro-4-(4-ethyl-1H-imidazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(S)-N-[[3-[3-Fluoro-4-[4-(carbomethoxy)-1H-imidazol-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(S)-N-[[3-[3-Fluoro-4-[4-(hydroxymethyl)-1H-imidazol-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(S)-N-[[3-[3-Fluoro-4-[4-(2-hydroxyethyl)-1H-imidazol-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(S)-N-[[3-[3-Fluoro-4-[1H-imidazol-1-yl-4-carboxaldehyde]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(S)-N-[[3-[3-Fluoro-4-[3-(hydroxyiminomethyl)-1H-imidazol-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(S)-N-[[3-[3-Fluoro-4-[3-(methoxyiminomethyl)-1H-imidazol-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(S)-N-[[3-[3-Fluoro-4-(1H-pyazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(S)-N-[[3-[3-Fluoro-4-(4-methyl-1H-pyazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(S)-N-[[3-[3-Fluoro-4-[3-(hydroxymethyl)-1H-pyazol-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;
(S)-N-[[3-[3-Fluoro-4-[3-(carbomethoxy)-1H-pyazol-1-yl]phenyl]-2-oxo-5-

oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(1H-pyazol-1-yl-3-carboxaldehyde)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(3-(hydroxyiminomethyl)-1H-pyazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(3-(methoxyiminomethyl)-1H-pyazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-[4-(hydroxymethyl)-1H-pyazol-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-[4-(carbomethoxy)-1H-pyazol-1-yl]phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(1H-pyazol-1-yl-4-carboxaldehyde)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(4-(hydroxyiminomethyl)-1H-pyazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(4-(methoxyiminomethyl)-1H-pyazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(1H-1,2,4-triazole-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[3-[3-Fluoro-4-[3-mercapto-4H-1,2,4-triazol-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methylacetamide;

(S)-N-[3-[3-Fluoro-4-[3-methylthio-4H-1,2,4-triazol-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methylacetamide;

(S)-N-[3-[3-Fluoro-4-[4H-1,2,4-triazol-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methylacetamide;

(S)-N-[[3-[3-Fluoro-4-(1H-1,2,3-triazole-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(4-carbomethoxy-1H-1,2,3-triazole-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(4-(hydroxymethyl)-1H-1,2,3-triazole-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(4-(1-hydroxyethyl)-1H-1,2,3-triazole-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(1H-1,2,3-triazole-1-yl-4-carboxaldehyde)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(4-(hydroxyiminomethyl)-1H-1,2,3-triazole-1-yl)phenyl]-2-oxo-5-

oxazolidinyl]methyl]acetamide, oxime;

(S)-N-[[3-[3-Fluoro-4-(4-(methoxyiminomethyl)-1H-1,2,3-triazole-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(4-acetyl-1H-1,2,3-triazole-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(4-(1-hydroxyiminoethyl)-1H-1,2,3-triazole-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(4-(1-methoxyiminoethyl)-1H-1,2,3-triazole-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(2H-1,2,3-triazole-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(1H-1,2,3,4-tetrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(2H-1,2,3,4-tetrazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(1H-indol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(7-aza-1H-indol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(1H-benzimidazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(1H-indazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

(S)-N-[[3-[3-Fluoro-4-(1H-benzotriazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; and

(S)-N-[[3-[3-Fluoro-4-(1H-1,2,3-triazolo[4,5*b*]-pyridin-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

Antibacterial Activity

The oxazolidinone antibacterial agents of this invention have useful activity against a variety of organisms. The *in vitro* activity of compounds of this invention can be assessed by standard testing procedures such as the determination of minimum inhibitory concentration (MIC) by agar dilution as desribed in "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically" (MFT) published January 1983 by the National Committee for Clinical Laboratory Standards, 771 East Lancaster Avenue, Villanova, Pennsylvania 19084, USA. The activity of selected compounds of this invention against *Staphylococcus aureus* and *Streptococcus pneumoniae* are shown in Table 1.

Table 1. *In vitro* **Activities: Minimum Inhibitory Concentrations (μg/mL).**

Example No.	*S. aureus*, UC®9213	*S. pneumoniae*, UC®9912
1	<0.5	<0.5
2	2	1
3	2	<0.5
4	4	1
5	4	1
6	1	<0.5
7	1	<0.5
8	4	1
9	>32	8
10	8	1
11	>16	1
12	0.25	<0.06
13	.1	0.25
14	2	0.25
15	1	0.25
16	1	<0.25
17	1	0.5
18	4	0.5
19	4	0.5
20	4	1
21	0.5	0.25
22	8	0.5
23	4	0.5
24	4	0.5
25	4	0.5
26	8	0.5
Vancomycin	1	0.5

Antimicrobial activity was tested in vivo using the Murine Assay procedure. Groups of female mice (six mice of 18-20 grams each) were injected intraperitoneally with bacteria which were thawed just prior to use and suspended in brain heart infusion with 4% brewers yeast **UC9213** (*Staphylococcus aureus*) or brain heart infusion (Streptococcus species). Antibiotic treatment at six dose levels per drug was administered one hour and five hours after infection by either oral intubation or subcutaneous ("subcut.") routes. Survival was observed daily for six days. ED_{50} values based on mortality ratios were calculated using probit analysis. The subject compounds were compared against a well-known antimicrobial (Vancomycin) as a control. The data are shown in Table 2.

Table 2. *In vivo* Activities: ED_{50}(mg/Kg).

Example No.	*S. aureus*,UC®9213	Control, ED_{50}
3	9.5	vancomycin, 2.2
4	5.7	vancomycin, 2.4
6	4.7	vancomycin, 2.0
7	11.9	vancomycin, 1.2
15	7.3	--
16	5.5	--

EXAMPLES

Example 1: (S)-N-[[3-[3-Fluro-4-(1H-pyrrol-1-yl)phenyl]-2-oxo-5-oxazoldinyl] methyl]acetamide:

3-Fluoro-1-nitro-4-(1H-pyrrol-1-yl)benzene:

A slurry of 403mg(630mg of 60% in oil, 15.75mmol) of sodium hydride in 85mL THF was treated with 1.01g(1.04mL, 15mmol) of pyrrole, followed by warming at 50°C foe 15min. The solution was then treated with 2.51g(1.74mL, 15.75mmol) of 3.4-difluoronitrobenzene, followed by warming at reflux for 18h. The mixture was then cooled and treated with 10mL saturated ammonium chloride solution. The mixture was diluted with ethyl acetate and extracted with water (2x). Drying

(Na_2SO_4) and concentration *in vacuo* afforded a dark brown solid, which was chromatographed over 75g of 230-400 mesh silica gel, eluting with 30%(v/v) dichloromethane in hexane. These procedures afforded 2.05g(66%) of the title pyrrole derivative as a light yellow solid. ^{1}H NMR ($CDCl_3$): δ8.14, 7.57, 7.16, 6.44.

3-Fluoro-1-(phenylmethoxycarbonylamino)-4-(1H-pyrrol-1-yl)benzene:

A solution of 500mg(2.43mmol) of the previous pyrrole derivative in 50mL of 4:1 THF-water was treated with 75mg of 5% platinum on sulfide carbon followed by hydrogenation at one atmosphere for 18h. The mixture was then treated with 10mL saturated $NaHCO_3$ solution and cooled to -20°C. The mixture was treated with 477mg(0.42mL, 2.79mmol) of benzyl chloroformate followed by warming to ambient temperature for 48h. The mixture was filtered through celite, washing the filter cake with methanol. The mixture was concentrated to *ca*. half the original volume, and the mixture was diluted with ethyl acetate and extracted with water (4 x) and saturated NaCl solution. Drying (Na_2SO_4) and concentration *in vacuo* afforded a brown solid, which was chromatographed over 35g 230-400mesh silica gel, eluting with 1:3:32 methanol- dichloromethane-hexane, and then with 1:3:16 methanol-dichloromethane-hexane. These procedures afforded 581mg of the title CBZ derivative as a brown solid, suitable for use in the next step. ^{1}H NMR ($CDCl_3$): 7.50, 7.40, 7.30, 7.09, 6.98, 6.35, 5.23.

(S)-[3-[3-Fluoro-4-(1H-pyrrol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methanol:

A solution of 300mg(0.97mmol) of CBZ derivative **2** in 5mL THF at -78°C was treated with 1.06mL(1.0*M*, 1.06mmol) of lithium bis(trimethylsilyl)amide followed by stirring at -78°C for 30min. The solution was treated with 153mg(0.15mmol) of (R)-(-)-glycidiyl butyrate followed by warming to 0°C and then gradual warming to ambient temperature for 48h. The mixture was diluted with ethyl acetate and extracted with water and saturated NaCl solution. Drying (Na_2SO_4) and concentration *in vacuo* afforded a red-brown oil which was subjected to radial chromatography on a 2mm chromatotron plate, eluting with 2%(v/v) methanol in dichloromethane and then with 5%(v/v) methanol in dichloromethane. These procedures afforded 157mg(59%) of the title oxazoldinone as a light tan solid. High Resolution Mass Spectrum: Calculated For $C_{14}H_{13}FN_2O_3$: 276.0910. Found: 276.0918.

(S)-[3-[3-Fluoro-4-(1H-pyrrol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl azide:

A solution of 1.94g(7.0mmol) of the previous alcohol and 1.24g(1.71mL, 12.25mmol) of triethylamine in 60mL dichloromethane at 0°C was treated with

1.0g(0.68mL, 8.78mmol) of methanesulfonyl chloride, followed by stirring at 0°C for 30min. The solution was warmed to ambient temperature and diluted with dichloromethane, followed by extraction with water (3x) and saturated NaCl solution. Drying(Na_2SO_4) and concentration *in vacuo* afforded an amber oil which was dissolved in 120mL DMF, treated with 4.5g(70mmol) of sodium azide and warmed at 60°C for 18h. The mixture was cooled and diluted with 75mL of 1:1 ether-ethyl acetate and extracted with water (6 x 40mL). Drying (Na_2SO_4) and concentration *in vacuo* afforded 2.13g(100%) of the title azide as a yellow-brown solid, sufficiently pure for use in the next step. High Resolution Mass Spectrum: Calculated For $C_{14}H_{12}FN_5O_2$: 302.1053. Found: 302.1056.

(S)-N-[[3-[3-Fluro-4-(1H-pyrrol-1-yl)phenyl]-2-oxo-5-oxazoldinyl] methyl]acetamide:

A solution of 1.0g(3.32mmol) of the previous azide in 30mL methanol and 15mL THF was treated with 200mg of platinum on sulfide carbon followed by hydrogenation at one atmosphere for 24h. The solution was filtered though celite, washing the filter cake with THF. The filtrate was concentrated *in vacuo* and the residue was dissolved in pyridine and treated with acetic anhydride followed by stirring at ambient temperature for 48h. The solution was concentrated under high vacuum, and the brown solid obtatined was dissolved in ethyl acetate and extracted with water (2x). Drying (Na_2SO_4) and concentration *in vacuo* afforded a brown solid which was chromatographed over 50g of 230-400mesh silica gel, eluting with 1%(v/v) methanol in dichloromethane and then with 2%(v/v) methanol in dichloromethane. These procedures afforded 582mg(56%) of the title compound as an off-white solid, mp 198-199.5°C. High Resolution Mass Spectrum: Calculated For CHFNO: 317.1176. Found: 317.1182.

Example 2: (S)-N-[[3-[3-Fluoro-4-(1H-pyrazol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide:

3-Fluoro-1-nitro-4-(1H-pyrazol-1-yl)benzene:

A solution of 2.0g(29.37mmol) of pyrazole and 8.12g(58.75mmol) of potassium carbonate in 70mL of DMSO was treated with 4.67g(3.25mL, 29.37mmol) of 3, 4-difluoronitrobenzene followed by warming at 90°C for 18h. The solution was cooled and diluted with 100mL water and was extracted with ethyl acetate (2 x 100mL). The organic layers were extracted with water (5 x 100mL) and with saturated NaCl solution (75mL). Drying (Na_2SO_4) and concentration *in vacuo* afforded an off-white solid which was recrystallized from hot hexanes to afford 5.3g(87%) of the title

pyrazole derivative as an off- white solid, mp 128-129°C.

3-Fluoro-1-(phenylmethoxycarbonylamino)-4-(1H-pyrazol-1-yl)benzene:

A solution of the previously prepared pyrazole in 120mL THF was treated with 1.5g of W-2 Raney Nickel followed by hydrogenation under 40psi of hydrogen for 16h. The solution was filtered through celite, washing the filter cake with acetone, and concentration of the filtrate *in vacuo*. The yellow residue obtained was dissolved in 100mL THF and treated with 75mL saturated $NaHCO_3$ solution, followed by cooling to 0°C. The solution was then treated with 7.30g(42.72mmol) of benzyl chloroformate followed by stirring at 0°C for 30 min and then by warming to ambient temperature for 1h. The mixture was diluted with 125mL ethyl acetate and 100mL water. The layers were separated and the aqueous layer was extracted with 100ml ethyl acetate. The combined organic layers were extracted with saturated $NaHCO_3$ solution (2 x 100mL) and saturated NaCl solution. Drying (Na_2SO_4) and concentration *in vacuo* afforded a light beige solid, which was recrystallized from chloroform-hexane to afford 5.92g(79%) of the title compound as glistening white plates, mp 82-83°C.

(S)-[3-[3-fluoro-4-(1H-pyrazol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methanol:

A solution of 3.0g(9.63mmol) of the CBZ derivative **2** in 130mL THF at -78°C was treated with 10.6mL(1.0*M*, 10.60mmol) of lithium bis(trimethylsilyl)amide in THF followed by stirring at -78°C for 30min. The solution was then treated with 1.53g(1.50mL, 10.60mmol) of neat (R)-(-)-glycidiyl butyrate, followed by stirring at -78°C for 30min and then warming to ambient temperature for 18h. The mixture was treated with 2mL saturated ammonium chloride solution, followed by dilution with 400mL ethyl acetate. The mixture was extracted with water (2 x 100mL) and saturated NaCl solution (200mL). Drying (Na_2SO_4) and concentration *in vacuo* afforded a yellow solid which was recrystallized from hot methanol to afford 2.28g(85%) of compound **3** as fine white needles, mp 180-181°C.

(S)-[3-[3-Fluoro-4-(1H-pyrazol-1yl)phenyl]-2-oxo-5-oxazolidinyl]methyl methanesulfonate:

A slurry of 403mg(1.45mmol) of the previously prepared compound and 882mg(1.22mL, 8.71mmol) of triethylamine in 15mL dichloromethane at 0°C was treated with 500mg(0.34ml, 4.36mmol) of methanesulfonyl chloride dropwise. The solution was stirred at 0°C for 30 min, followed by warming to ambient temperature. The mixture was diluted with 20mL dichloromethane and extracted with water (2 x 25mL) and saturated $NaHCO_3$ solution. Drying (Na_2SO_4) and concentration *in vacuo* afforded 520mg(*ca.* 100%) of the title mesylate, sufficiently

pure for further use. ^1H NMR (DMSO-d_6): δ8.16, 7.80, 7.48, 6.55, 5.05, 4.53, 4.23, 3.89, 3.25.

(S)-[3-[3-Fluoro-4-(1H-pyrazol-1yl)phenyl]-2-oxo-5-oxazolidinyl]methylazide:

A solution of 518mg(1.45 mmol) of the previous mesylate in 15mL N, N-dimethylformamide was treated with 1.89g(29.07mmol) of sodium azide followed by warming at 70°C for 48h. The mixture was diluted with 100mL ethyl acetate followed by extraction with water (6 x 75mL) and saturated NaCl solution (75mL). Drying (Na_2SO_4) and concentration *in vacuo* afforded a beige solid which was chromatographed over 50g of 230-400 mesh silica gel, eluting with 3%(v/v) acetone in dichloromethane and then with 3.5%(v/v) methanol in dichloromethane. These procedures afforded 355mg(81%) of the title azide as a white solid. ^1H NMR ($CDCl_3$): δ7.99, 7.92, 7.76, 7.24, 6.49, 4.83, 4.12, 3.99, 3.74, 3.62.

(S)-N-[[3-[3-Fluoro-4-(1H-pyrazol-1-yl)phenyl]-2-oxo-5-oxazoldinyl] methyl]acetamide:

A solution of 355mg of the previous azide in 30mL ethyl acetate was treated with 150mg of palladium on calcium carbonate followed by hydrogenation at one atmosphere for 18h. The solution was then treated with 15mL pyridine and 10mL acetic anhydride followed by stirring at ambient temperature for 18h. The mixture was diluted with 100mL ethyl acetate and filtered through celite, washing the filter cake with ethyl acetate. The mixture was concentrated *in vacuo*, and the remaining pyridine and acetic anhydride removed by short path distillation under high vacuum (0.2mmHg/ hot water bath). The solid residue obtained was recrystallized from hot acetone-hexane to afford 192mg(51%) of the title compound as a white solid, mp 183-184°C.

Example 3: (S)-N-[[3-[3-Fluoro-4-(1H-imidazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

3-Fluoro-4-(1H-imidazol-1-yl)nitrobenzene:

A solution of 2.14g(31.4mmol) of imidazole and 10.9g(62.8mmol) of dibasic potassium phosphate in 190mL DMSO was treated with 5.25g(3.7mL, 32.9mmol) of 3,4-difluoronitrobenzene followed by warming at 90°C for 18h. The solution was diluted with ethyl acetate and was extracted with water. The water layer was back-extracted with ethyl acetate and the combined organic layers were then extracted with water (2x). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford a brown solid. This material was chromatographed over 250g of 230-400mesh

silica gel, eluting with dichloromethane, and then with 1%(v/v) methanol in dichloromethane, and finally with 2%(v/v) methanol in dichloromethane. These procedures afforded 6.0g(92%) of the title compound as a bronze colored solid. ^1H NMR ($CDCl_3$): δ8.17, 7.96, 7.63, 7.35, 7.26.

3-Fluoro-4-(1H-imidazol-1-yl)-1-(phenylmethoxycarbonylamino)benzene:

A solution of 500mg(2.41mmol) of the previous nitro compound in 50mL THF was treated with 100mg of 10% palladium on carbon, followed by hydrogenation at atmospheric pressure for 20h. The mixture was treated with 60mg of additional 10% palladium on carbon and hydrogenation at atmospheric pressure was continued for 5h. The mixture was then filtered through celite washing the filter cake with methanol. The filtrate was concentrated *in vacuo* to afford a brown oil, which was dissolved in 50mL anhydrous THF, followed by treatment with 405mg(4.82mmol) of solid sodium bicarbonate. The solution was cooled to -20°C, followed by addition of 493mg(0.43mL, 2.89mmol) of benzyl chloroformate dropwise. The mixture was warmed to ambient temperature for 18h, followed by dilution with ethyl acetate. The solution was extracted with water (3x) and saturated sodium chloride solution. Drying (Na_2SO_4) and concentration *in vacuo* afforded a light brown solid which was recrystallized from hot chloroform-hexane to afford 692mg(92%) of the title compound as light brown crystals. High Resolution Mass Spectrum: Calculated for $C_{17}H_{14}FN_3O_2$: 311.1070. Found: 311.1092.

(S)-[3-[3-Fluoro-4-(1H-imidazol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methanol:

A solution of 500mg(1.61mmol) of the previous CBZ derivative in 22mL THF and 4mL DMF at -78°C was treated with 1.69mL(1.69mmol) of lithium bis(trimethylsilyl)amide followed by stirring at -78°C for 20 min. The solution was treated with 243mg(0.24mL, 1.69mmol) of (R)-(-)-glycidyl butyrate followed by warming to 0°C and then to ambient temperature. After stirring 3h at ambient temperature, TLC evidence suggested that no reaction had occurred. The solution was then warmed at 40°C for 2h, followed by cooling and stirring at ambient temperature for 18h. The solution was then diluted with ethyl acetate and extracted with water (3x). Drying (Na_2SO_4) and concentration *in vacuo* afforded a brown solid. This material was chromatographed over 40g of 230-400 mesh silica gel eluting with 2%(v/v) methanol in dichloromethane and then with 5%(v/v) methanol in dichloromethane. These procedures afforded 214mg(48%) of the title compound as a light yellow solid. High Resolution Mass Spectrum: Calculated For $C_{13}H_{12}FN_3O_3$: 277.0863. Found: 277.0876.

(S)-[3-[3-Fluoro-4-(1H-imidazol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methylazide:

A solution of 150mg(0.54mmol) of the previous oxazolidinone and 96mg(0.13mL, 0.95mmol) of triethylamine in 5mL dichloromethane at 0°C was treated with 77mg(52μL, 0.68mmol) of methanesulfonyl chloride, followed by stirring at 0°C for 30min. The solution was warmed to ambient temperature followed by dilution with dichloromethane and extraction with water (3x). Drying (Na_2SO_4) and concentration *in vacuo* afforded a light brown foam. This material was dissolved in 10mL DMF and treated with 525mg(8.1mmol) of sodium azide, followed by warming at 60°C for 48h. The solution was cooled and diluted with ethyl acetate followed by extraction with water (3x). Drying (Na_2SO_4) and concentration *in vacuo* afforded 163mg(100%) of the title azide as a yellow oil. ^{1}H NMR ($CDCl_3$): δ8.15, 7.74, 7.46, 7.35, 7.29, 4.85, 4.12, 3.90, 3.76, 3.59.

(S)-N-[[3-[3-Fluoro-4-(1H-imidazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl] methyl]acetamide:

A solution of 163mg(0.54mmol) of the azide in 8mL pyridine was treated with 85mg of palladium on calcium carbonate and 110mg(0.10mL, 1.08mmol) of acetic anhydride. This mixture was hydogenated at one atmosphere for 20h. The mixture was then treated with 80mg of palladium on calcium carbonate followed by hydrogenation at one atmosphere for 4h. The solution was filtered through celite, washing the filter cake with ethyl acetate. The filtrate was concentrated under high vacuum, and the residue was subjected to radial chromatography on a 2mm chromatotron plate eluting with 2%(v/v) methanol in dichloromethane and then with 5%(v/v) methanol in dichloromethane. These procedures afforded 84mg(49%) of the title compound as a white solid. High Resolution Mass Spectrum: Calculated For $C_{15}H_{15}FN_4O_3$: 318.1128. Found: 318.1140.

Example 4: (S)-N-[[3-[3-Fluoro-4-(1H-1,2,4-triazol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide:

3-Fluoro-1-nitro-4-(1H-1,2,4-triazol-1-yl)benzene:

A solution of 5.0g(72.4mmol) of 1H-1,2,4-triazole and 25.22g(144.8mmol) of dibasic potassium phosphate in 150mL DMSO was treated with 11.52g(72.4mmol) of 3,4-difluoronitrobenzene followed by warming at 90°C for 3h. The solution was cooled and added to 500mL water, and the resulting white solid was collected by filtration and washed with water. The white solid obtained was dried *in vacuo* (60°C/10mmHg) to afford 10.79g(72%) of the title compound as a white solid. High

Resolution Mass Spectrum: Calculated for $C_8H_5FN_4O_2$: 208.0396. Found: 208.0408.

3-Fluoro-4-(1H-1,2,4-triazol-1-yl)aniline:

A solution of 8.7g(41.83mmol) of the previous nitro compound in 350mL of 1:1 methanol-THF was treated with 3.5g of 10% palladium on carbon followed by hydrogenation under 45psi of hydrogen pressure for 18h. The solution was filtered through celite, washing the filter cake with methanol. The filtrate was concentrated *in vacuo* and the residue obtained was chromatographed over 200g of 230-400mesh silica gel eluting with 1%(v/v) methanol in dichloromethane and then with 3%(v/v) methanol in dichloromethane. These procedures afforded 4.0g(54%) of the aniline derivative as an off-white solid. High Resolution Mass Spectrum: Calculated for $C_8H_7FN_4$: 178.0655. Found: 178.0673.

3-Fluoro-1-(phenylmethoxycarbonylamino)-4-(1H-1,2,4-triazol-1-yl)benzene:

A solution of 4.0g(22.5mmol) of the previous aniline derivative in 50mL acetone was treated with 50mL of saturated $NaHCO_3$ solution, followed by cooling to 0°C. The solution was treated with 8.0g(6.78mL, 47.26mmol) of benzyl chloroformate. The solution was warmed to ambient temperature for 1h, followed by addition to 300mL water and extraction with ethyl acetate (2 x300mL). The organic layer was extracted with 300mL water and dried (Na_2SO_4). Concentration *in vacuo* afforded a beige solid which was recrystallized from chloroform-hexane to afford 2.6g(37%) of the title CBZ derivative. High Resolution Mass Spectrum: Calculated for $C_{16}H_{13}FN_4O_2$: 312.1022. Found: 312.1033.

(S)-[3-[3-Fluoro-4-(1H-1,2,4-triazol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methanol:

A solution of 2.5g(8.0mmol) of the previously prepared CBZ derivative in 115mL THF at -78°C was treated with 8.8mL(1.0*M*, 8.8mmol) of lithium bis(trimethylsilyl)amide, followed by stirring at -78°C for 30min. The solution was then treated with 1.27g(1.25mL, 8.8mmol) of (R)-(-)-glycidiyl butyrate, followed by stirring at -78°C for 15min. The solution was then warmed to ambient temperature for 18h. The mixture was treated with 2mL saturated ammonium chloride solution, followed by dilution with 100ml water and extraction with ethyl acetate (2 x 100mL). Drying (Na_2SO_4) and concentration *in vacuo* afforded a semi-solid, which was triturated with chloroform to provide 1.4g(57%) of the title oxazolidinone. High Resolution Mass Spectrum: Calculated for $C_{12}H_{11}FN_4O_3$: 278.0815. Found: 278.0836.

(S)-[3-[3-Fluoro-4-(1H-1,2,4-triazol-1-yl)phenyl]-2-oxo-5-oxazoldinyl] methylazide:

A slurry of 1.0g(3.6mmol) of the previously prepared oxazolidinone and 548mg(0.76mL, 5.42mmol) of triethylamine in 20mL dichloromethane at 0°C was treated with 495mg(0.33mL, 4.32mmol) of methanesulfonyl chloride. The solution was then warmed to ambient temperature for 2h. The solution was then treated with 20mL water and the layers separated. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford 1.0g(75%) of the the intermediate mesylate as a tan solid. A soution of 1.34g(3.6mmol) of this material and 2.34g(36mmol) of sodium azide in 36mL of DMF was warmed at 70°C for 18h. The solution was cooled and diluted with 100mL ethyl acetate, followed by extraction with water (5 x 75mL). Drying (Na_2SO_4) and concentration *in vacuo* afforded 1g(88%) of the title azide as an off- white solid. ^{1}H NMR Spectrum ($CDCl_3$): δ8.65, 8.13, 7.91, 7.83, 7.32, 4.85, 4.14, 3.92, 3.77, 3.63.

(S)-N-[[3-[3-Fluoro-4-(1H-1,2,4-triazol-1-yl)phenyl]-2-oxo-5-oxazoldinyl] methyl]acetamide:

A solution of 100mg(0.36mmol) of the azide in 3ml pyridine was treated with 50mg of palladium on calcium carbonate followed by hydrogenation at one atmosphere for 18h. The solution was treated with 0.2mL acetic anhydride followed by stirring at ambeient temperature for 18h. The solvent was removed *in vacuo* and the residue dissolved in ethyl acetate and extracted with water. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to afford a light beige solid. This material was subjected to radial chromatography on a 2mm plate eluting with 2%(v/v) methanol in dichloromethane and then with 4%(v/v) methanol in dichloromethane. These procedures afforded 62mg(54%) of the title compound as a white solid. High Resolution Mass Spectrum: Calculated for $C_{14}H_{14}FN_5O_3$: 319.1018. Found: 319.1087.

Example 5: (S)-N-[[3-[3-Fluoro-4-(1H-indol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

3-Fluoro-4-(1H-indol-1-yl)nitrobenzene:

A slurry of 334mg(374mg of 60% in oil, 9.35mmol) of sodium hydride in 5mL THF was treated with a solution of 1.0g(8.5mmol) of indole in 5mL THF, followed by stirring at ambient temperature for 15min. The solution was then treated with 1.35g(8.5mmol) of 3,4-difluoronitrobenzene. The solution was stirred at ambient temperature for 48h, followed by concentration *in vacuo* to afford brown oil which was dissolved in ethyl acetate and washed with water. Drying (Na_2SO_4) and

concentration *in vacuo* afforded an oil which was chromatographed over 100g of 230-400mesh silica gel, eluting with 20%(v/v) ethyl acetate in hexane. These procedures afforded 1.1g(51%) of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$): δ8.23, 7.74, 7.40, 7.35, 7.30, 6.80.

3-Fluoro-4-(1H-indole-1-yl)-1-(phenylmethoxycarbonylamino)benzene:

A solution of 1.0g(3.9mmol) of the previously prepared nitro compound in 5mL THF was treated with 200mg of W-2 Raney nickel followed by hydrogenation at one atmosphere for 18h. The solution was filtered through celite, washing the filter cake with THF. The filtrate was concentrated *in vacuo* and the residue dissolved in 10mL acetone and treated with 8.2mL saturated $NaHCO_3$ solution, followed by cooling to 0°C and addition of 699mg(4.1mmol) of benzyl chloroformate. The solution was warmed to ambient temperature for 18h, diluted with ethyl acetate and extracted with water. Drying (Na_2SO_4) and concentration *in vacuo* afforded an oil, which was chromatographed over 75g of 230-400 mesh silica gel, eluting with 50%(v/v) ethyl acetate in hexane. These procedures afforded 1.03g(71%) of the title compound as a yellow solid. ^{1}H NMR ($CDCl_3$): δ7.69, 7.60, 7.40, 7.25, 7.15, 6.70.

(S)-[3-[3-Fluoro-4-(1H-indol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methanol:

A solution of 1.0g(2.77mmol) of the previous CBZ derivative in 5mL THF at -78°C was treated with 3.05mL(1.0M, 3.05mmol) of lithium bis(trimethylsilyl)amide in THF followed by stirring at -78°C for 45min. The solution was treated with 440mg(0.43mL, 3.05mmol) of (R)-(-)-glycidiyl butyrate followed by stirring at -78°C for 15min, warming to 0°C for 15min and finally warming to ambient temperature for 18h. The mixture was diluted with ethyl acetate and extracted with water. Drying (Na_2SO_4) and concentration *in vacuo* afforded a semisolid which was chromatographed over 60g of 230-400mesh silica gel, eluting with 2%(v/v) methanol in dichloromethane. These procedures afforded 630mg(70%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$): δ7.69, 7.50, 7.38, 7.25, 6.71, 4.80, 4.09, 3.79.

(S)-[3-[3-Fluoro-4-(1H-indol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methylazide:

A solution of 484mg(1.2mmol) of the previous mesylate in10mL DMF was treated with 390mg(6mmol) of sodium azide followed by warming at 90°C for 18h. The solution was cooled and diluted with ethyl acetate and extracted with water. Drying (Na_2SO_4) and concentration *in vacuo* afforded 336mg(80%) of the title azide as a gum, sufficiently pure for further use. ^{1}H NMR ($CDCl_3$): δ7.72, 7.68, 7.51, 7.37, 7.20, 6.71, 4.85, 4.13, 3.91, 3.77, 3.62.

(S)-N-[[3-[3-Fluoro-4-(1H-indol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]

acetamide:

A solution of 336mg(0.96mmol) of the previous azide in 5mL ethyl acetate was treated with 150mg of 10% palladium on carbon followed by hydrogenation at one atomosphere for 18h. The solution was filtered through celite, washing the filter cake with ethyl acetate. The filtrate was concentrated *in vacuo* to afford a light brown oil which was dissolved in 2mL pyridine and treated with 0.2mL acetic anhydride, followed by stirring at ambient temperature for 60h. The solution was concentrated under high vacuum, and the residue was dissolved in chloroform and extracted with water. Drying (Na_2SO_4) and concentration *in vacuo* afforded a gum which was subjected to radial chromatography on a 4mm chromatotron plate, eluting with 1.5%(v/v) methanol in dichloromethane and then with 2.5%(v/v) methanol in dichloromethane. These procedures afforded 277mg(81%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$): δ7.70, 7.51, 7.33, 7.20, 6.71, 6.11, 4.84, 4.12, 3.87, 3.70, 2.06.

Example 6: (S)-N-[[3-[3-Fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

3-Fluoro-1-nitro-4-(1H-1,2,3-triazol-1-yl)benzene:

A slurry of dibasic potassium phosphate, 38.0 g (0.218 mol), and 1H-1,2,3-triazole, 7.53 g (6.3 mL, 0.109 mol), in 325 mL dimethylsulfoxide was treated dropwise with 3,4-difluoronitrobenzene, 17.3 g (12.1 mL, 0.109 mol), with heating to 90°C for 18 h. The mixture was cooled to room temperature, diluted with water (500 mL) and extracted with ethyl acetate (4 x 50 mL). Drying (Na_2SO_4) and concentrating *in vacuo* afforded a light yellow solid. This material was chromatographed over 600 g 230-400 mesh silica gel eluting with methylene chloride, 1% (v:v), 2% (v:v) and 5%(v:v) methanol-methylene chloride to afford 11.38 g (50%) of 3-Fluoro-1-nitro-4-(1H-1,2,3-triazol-1-yl)benzene as a light yellow solid, mp =123-124.5°C, along with 9.66 g (43%) of regioisomer 3-Fluoro-1-nitro-4-(2H-1,2,3-triazol-2-yl)benzene as a light yellow solid, mp 137-139°C.

3-Fluoro-1-(phenylmethoxycarbonylamino)-4-(1H-1,2,3-triazol-1-yl)benzene:

A solution of 5.0 g (24.0 mmol) of the previous compound in 400 mL of 1:1 methanol-THF was treated with 3g of W-2 Raney nickel. The mixture was hydrogenated on a Parr shaker under 45 psi hydrogen pressure for 18 h followed by filtering through celite, washing the filter cake with methanol. Concentration *in vacuo* afforded a white solid which was dissolved in 500 mL anhydrous THF, cooled

to -20°C and treated with sodium bicarbonate, 4.0 g (48.0 mmol) and benzyl chloroformate, 4.9 g (4.3 mL, 28.8 mmol). After stirring 72 h with gradual warming to room temperature, the solvent was removed under reduced pressure and the resulting oil was dissolved in 200 mL ethyl acetate. The mixture was extracted with water (3 x 50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow solid. This material was cchromatographed over 400 g 230-400 mesh silica gel eluting with methylene chloride, 1% (v:v) and 2% (v:v) methanol-methylene chloride to afford 6.18 g (82%) of the title compound as a white solid, mp 121-122°C.

(R)-[3-[3-Fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methanol:

A solution of 2.0 g (6.4 mmol) of the previous compound in 100 mL anhydrous THF at -78°C was treated with 6.7 mL(1.0M, 6.7 mmol) of lithium bis(trimethylsilyl)amide in THF followed by stirring at -78 °C for 30 minutes. The mixture was treated with 960 mg(6.7 mmol) of *R*-(-)-glycidyl butyrate, followed by warming to 0°C with gradual warming to room temperature. After 18 h, the mixture was quenched with saturated aqueous ammonium chloride (30 mL) and extracted with ethyl acetate (3 x 30 mL). Drying (Na_2SO_4) and concentration *in vacuo* gave a yellow oily solid. The crude material was recrystallized from boiling 2:1 methanol-ethyl acetate to afford 1.10 g (62%) of the title compound as a white solid, mp 179-180.5°C.

(R)-[3-[3-Fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methylazide:

A slurry of 1.35 g(4.85 mmol) of the previous compound and 859 mg (1.18 mL, 8.49 mmol) triethylamine in 60 mL dichloromethane at 0°C was treated with 695 mg(0.47 mL, 6.07 mmol) methanesulfonylchloride followed by warming to ambient temperature over 1 h. The mixture was then cooled to 0°C, treated with triethylamine, 859 mg (8.49 mmol), and methanesulfonyl chloride, 695 mg (6.07 mmol). After 5 minutes, the mixture was extracted with water (3 x 20 mL), saturated aqueous sodium bicarbonate (2 x 20 mL) and saturated aqueous sodium chloride (1 x 20 mL). Drying (Na_2SO_4) and concentration *in vacuo* afforded 1.89 g of the corresponding mesylate as a light yellow solid, which was dissolved in90 mL DMF and treated with 4.73g(72.8 mmol) sodium azide and warmed at 60°C for 18 h. The mixture was cooled to 0°C and diluted with water (200 mL). The mixture was extracted with 1:1 ethyl ether-ethyl acetate (5 x 50 mL). The combined organic layers were then extracted with water (4 x 50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford 1.48 g (ca. 100%) of the title azide as an off-white solid,

sufficiently pure for further use. ^{1}H NMR ($CDCl_3$) δ 8.09, 7.98, 7.87, 7.29, 4.86, 4.16, 3.94, 3.70.

(S)-N-[[3-[3-Fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

A solution of 300 mg(0.99 mmol) of the previous azide in 12 mL THF was treated with 750mg of W-2 Raney nickel. The mixture was hydrogenated at atmospheric pressure for 18 h. The mixture was treated with 783 mg (0.80 mL, 9.9 mmol) pyridine, and 505 mg (0.47 mL, 4.9 mmol) acetic anhydride followed by stirring for 2 h. The mixture was filtered through celite, washing the filter cake with ethyl acetate. The filtrate was extracted with water (3 x 30 mL) and saturated aqueous sodium chloride (1 x 20 mL). Drying (Na_2SO_4) and concentration *in vacuo* gave an off-white solid. The crude material was recrystallized from boiling 10:1 ethyl acetate-hexane to give 210mg(66%) of the title compound as a white solid, mp 193-194°C.

Example 7: (S)-N-[[3-[3-Fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-2,2-dichloroacetamide:

A solution of 275 mg (0.91 mmol) of (R)-[3-[3-Fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methylazide (from Example 6) in 15 mL THF was treated with 1..5g of W-2 Raney nickel, and hydrogenated at atmospheric pressure. After 18 h, the mixture was filtered through celite, washing the filter cake with methanol. The filtrate was concentrated *in vacuo* and the resulting oil was slurried in 15 mL methylene chloride, cooled to 0°C and treated with 138 mg(0.19 mL, 1.36 mmol) triethylamine, and 161mg(0.11 mL, 1.09 mmol) dichloroacetyl chloride . After stirring at ambient temperature for 24h, the mixture was diluted with methylene chloride and extracted with water (3 x 20 mL) and saturated aqueous sodium chloride (1 x 20 mL). Drying (Na_2SO_4) and concentration *in vacuo* afforded an off-white solid. The crude material was subjected to radial chromatography on a 4mm chromatotron plate eluting with dichloromethane and 2% (v/v) methanol-dichloromethane. These procedures afforded 182 mg (52%) of the title compound as a white solid, mp 195-198°C dec.

Example 8: (S)-N-[[3-[3-Fluoro-4-(2H-1,2,3-triazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

3-Fluoro-1-(phenylmethoxycarbonylamino)-4-(2H-1,2,3-triazol-2-yl)benzene:

A solution of 6.0g(28.82mmol) of 3-fluoro-1-nitro-4-(2H-1,2,3-triazol-2-yl)benzene in 150mL ethyl acetate and 25mL methanol was treated with 750mg of W-2 Raney Nickel. The mixture was hydrogenated on a Paar shaker under 45psi hydrogen pressure for 24h. The mixture was filtered through celite and the filtrate was concentrated in vacuo. The residue was dissolved in 150mL acetone, treated with 72mL saturated sodium bicarbonate solution, followed by cooling to 0 °C. The mixture was treated with 6.15g(5.14mL, 36.08mmol) of benzyl chloroformate, followed by stirring at 0 °C for 1h, and then warming to ambient temperature for 3h. The mixture was diluted with 500mL water and 400mL ethyl acetate. The aqueous phase was washed with 250mL ethyl acetate and the combined organic layers were extracted with 300mL saturated NaCl solution. Drying (Na_2SO_4) and concentration in vacuo afforded an amber oil which was recrystallized from hot chlorform-hexane to afford 7.52g(84%) of the title compound as a white solid, mp 99.5-101 °C.

(R)-[3-[3-Fluoro-4-(2H-1,2,3-triazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methanol:

A solution of 1.0g(3.20mmol) of the previous compound in 45mL THF at -78 °C was treated with 3.52mL(1.0M, 3.52mmol) of lithium bis-(trimethylsilyl)amide in THF, followed by stirring at -78 °C for 30min. The solution was treated with 508mg(0.50mL, 3.52mmol) of (R)-(-)-glycidiyl butyrate followed by stirring at 0 °C for 30min, and then to ambient temperature for 18h. The mixture was diluted with 75mL ethyl acetate and extracted with water (2 x 75mL) and saturated NaCl solution (75mL). Drying (Na_2SO_4) and concentration in vacuo afforded an amber oil, which was dissolved in 75ml of methanol and treated with 1.0g of K_2CO_3 followed by stirring for 2h. The mixture was filtered and concentrated in vacuo to afford an amber oil which was chromatographed over 50g of 230-400 mesh silica gel, eluting with 3% (v/v) methanol in dichloromethane. These procedures afforded 446(50%) of the title compound as a white solid, mp 159-151 °C.

(R)-[3-[3-Fluoro-4-(2H-1,2,3-triazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methylazide:

A solution of 350mg(1.26mmol) of the previous alcohol and 2mL of triethylamine in 8mL dichloromethane at 0 °C was treated with 362mg(1.64mmol) of nosyl chloride, followed by stirring at 0 °C for 30min, and warming to ambient temperature for 1h. The mixture was diluted with 50mL dichloromethane and was extracted with water (215.8g x 50mL). Drying (Na_2SO_4) and concentration in vacuo afforded 540mg(92%) of the corresponding nosylate, which was dissolved in 12mL

N,N-dimethylformamide and treated with 2g of sodium azide, followed by stirring at ambient temperature for 48h. The solution was dilutied with 125mL ethyl acetate and extracted with water (5 x 50mL). Drying (Na_2SO_4) and concentration in vacuo afforded a yellow solid, which was chromatographed over 50g of 230-400 mesh silica gel, eluting with dichloromethane and then with 5%(v/v) acetone in dichloromethane. These procedures afforded 333mg(94%) of the title azide as a faint yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.87, 7.70, 7.38, 4.84, 4.13, 3.91, 3.75, 3.63.

(S)-N-[[3-[3-Fluoro-4-(2H-1,2,3-triazol-2-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

A solution of the previous azide in 50mL ethyl acetate was treated with 500mg of W-2 Raney nickel followed by hydrogenation on a Paar shaker under 30psi of hydrogen for 18h. The mixture was filtered through celite, and the filtrated was concentrated in vacuo. The residue was dissolved in 8mL pyridine and treated with 4mL acetic anhydride followed by stirring at ambient temperature for 24h. The solvents were removed under high vacuum (0.2mm Hg) and the residue was dissolved in 75mL ethyl acetate and extracted with water (2 x 50mL) and saturated NaCl solution (50mL). Drying (Na_2SO_4) and concentration in vacuo afforded an amber oil which was subjected to radial chromatography on a 4mm chromatotron plate, eluting with 4%(v/v) methanol in dichloromethane. The material obtained was recrystallized from hot chloroform-hexane to afford 164mg(47%) of the title compound. ^{1}H NMR ($CDCl_3$) δ 7.87, 7.82, 7.70, 7.32, 6.21, 4.83, 4.10, 3.84, 3.68, 2.03.

Example 9: (S)-N-[[3-[3-Fluoro-4-(3-mercapto-4H-1,2,4-triazol-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

4-(N-Benzylamino)-3-fluoronitrobenzene:

A solution of 23.9g(16.9mL, 0.15mol) of 3,4-difluoronitrobenzene and 29.1g(39.2mL, 0.23mol) of N, N-diisopropylethylamine in 285mL acetonitrile was treated with 19.3g(19.7mL, 0.18mol) of benzylamine, followed by warming at reflux for 5h. The mixture was concentrated in vacuo and the residue was dissolved in 200mL ethyl acetate, followed by extraction with water (3 x 50mL). Drying (Na_2SO_4) and concentration in vacuo afforded a yellow solid, which was recrystallized from hot ethyl acetate-hexane to afford 32.25g(87%) of the title compound as yellow-orange needles, mp 97.5-99 ^{o}C.

4-(N-Benzylbenzyloxycarbonylamino)-1-(benzyloxycarbonylamino)-3-fluorobenzene:

A solution of 14.25g(0.058mol) of the previous compound in 800mL THF was treated with 1.0g of 5% platinum on carbon, followed by hydrogenation on a Parr shaker under 30psi hydrogen pressure for 18h. The mixture was filtered through celite, washing the filter cake with ethyl acetate. The filtrate was concentrated in vacuo to afford an oily residue which was dissolved in 1.0L of THF and treated with 15.8g(16.5mL, 0.13mol) of N, N-dimethylaniline. The solution was cooled to 0 °C and 21.72g(18.18mL, 0.127mol) of benzyl chloroformate was added dropwise over 3 min. The solution was stirred at 0°C for 30min and then was allowed to gradually warm to ambient temperature, followed by stirring for 23h. The solution was concentrated in vacuo and the residue was dissolved in 1L of ethyl acetate. The mixture was washed with 80mL cold 1N HCl solution, 80mL water, and 80mL saturated $NaHCO_3$ solution. The solution was dried ($MgSO_4$) and concentrated in vacuo to afford an oil which was chromatographed over 500g of 230-400 mesh silica gel, eluting with 10-15% (v/v) ethyl acetate in hexane. These procedures afforded 12.42g(44%) of the title compound as a white solid, mp 101-102.5 °C.

(R)-[3-[3-Fluoro-4-(N-benzylbenzyloxycarbonylamino)phenyl]-2-oxo-5-oxazolidinyl]methanol:

A solution of 12.42g(0.026mol) of the previous compound in 375mL THF at -78 °C was treated with 16.7mL(1.6M, 0.027mol) of n-butyllithium in hexanes dropwise over 6 min, followed by stirring at -78 °C for 30 min. The solution was then treated with 4..6g(4.5mL, 0.032mol) of (R)-(-)-glycidyl butyrate, followed by stirring at -78 °C for 1h, and warming to ambient temperature for 20h. The solution was treated with 25mL saturated ammonium chloride solution, followed by addition of 25mL water and 300mL ethyl acetate. The aqueous phase was extracted with ethyl acetate and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The oil obtained was chromatographed over 400g of 230-400 mesh silica gel, eluting with 1%(v/v) methanol in dichloromethane. These procedures afforded 7.56g(66%) of the title compound as a white solid. ^1H NMR ($CDCl_3$) δ 7.48, 7.25, 7.07, 6.95, 5.15, 4.18, 4.67, 3.91, 3.69.

(S)-N-[3-[3-Fluoro-4-(N-benzylbenzyloxycarbonylamino)phenyl]-2-oxo-5-oxazolidinyl]methylacetamide:

A solution of 8.23g(18.3mmol) of the prevous compound and 3.24g(4.5mL, 32.0mmol) of triethylamine in 107mL dichloromethane at 0°C was treated with 5.47g of nosyl chloride, followed by stirring at 0°C for 4h. The mixture was diluted with dichloromethane and extracted with water (2x). Drying (Na_2SO_4) and concentration in vacuo afforded a yellow foam, which was dissolved in 58ml

isopropyl alcohol, 93mL acetonitrile, and 116mL ammonium hydroxide, followed by warming at 40 °C for 18h. The mixture was cooled, diluted with ethyl acetate and extracted with water (3x) and saturated NaCl solution. Drying (Na_2SO_4) and concentration in vacuo afforded a yellow foam, which was dissolved in 200ml of ethyl acetate and treated with 4.67g(4.3mL, 45.75mmol) of pyridine and 7.24g(7.4mL, 91.5mmol) of acetic anhydride. The solution was stirred at ambient temperature for 18h, followed by extraction with water (3x) and saturated NaCl solution. Drying (Na_2SO_4) and concentration in vacuo afforded an amber foam, which was chromatographed over 450g of 230-400 mesh silica gel, eluting with 1%(v/v) methanol in dichloromethane. These procedures afforded 7.04g(78%) of the title compound as a light yellow rigid foam. High Resolution Mass Spectrum (EI): calcd for $C_{27}H_{26}FN_3O_5$: 491.1856. found: 491.1860.

(S)-N-[3-[3-Fluoro-4-aminophenyl]-2-oxo-5-oxazolidinyl]methylacetamide:

A solution of 5.6g(11.4mmol) of the previous compound in 200mL ethanol was treated with 200mg of 10% palladium on carbon, followed by hydrogenation on a Parr shaker under 45psi of hydrogen pressure for 24h. The mixture was filtered through celite, washing the filter cake with methanol. The filtrate was concentrated in vacuo to afford an off-white solid, which was recrystallized from hot ethyl acetate-hexane to afford 2.81g(92%) of the title compound as an off-white solid. ^1H NMR (DMSO) δ 8.20, 7.29, 6.95, 6.76, 5.00, 4.65, 4.00, 3.63, 3.37, 1.83.

(S)-N-[3-[3-Fluoro-4-isothiocyanophenyl]-2-oxo-5-oxazolidinyl]methylacetamide:

A solution of 960mg(4.12mmol) of 1,1'-thiocarbonyldi-2(1H)-pyridone in 30mL dichloromethane at 0 °C was treated with 1.0g(3.74mmol) of the previous compound in one portion. The mixture was stirred at 0 °C for 2.5h, followed by warming to ambient temperature for 2h. The mixture was concentrated in vacuo and the solid obtained was triturated with 15mL water. The product was collected by filtration and washed with a small amount of water, followed by drying overnight in a vacuum oven. These procedures afforded 1.09g(94%) of the title compound as a white solid, mp 172.5-176 °C.

(S)-N-[3-[3-Fluoro-4-[3-mercapto-4H-1,2,4-triazol-4-yl]phenyl]-2-oxo-5-oxazolidinyl]methylacetamide:

A solution of 1.11g(3.59mmol) of the previous compound in 26mL THF was treated with 230mg(3.77mmol) of formic hydrazide followed by warming at 70 °C for 3.5h. The mixture was cooled, and the precipitate was collected by filtration and washed with ethyl acetate. The solid was dried in a vacuum oven at 60 °C to afford

1.2g of a solid. Of this material, 100mg(0.27mmol) was suspended in 2mL water and treated with 0.28mL(0.97M, 0.27mmol) of KOH solution, followed by stirring for 45min. The solution was then treated with 0.28mL(1.0N, 0.28mmol) of HCl solution. The precipitate was collected by filtration and washed with a small amount of 1N HCl solution. The solid was dried in a vacuum oven at ambient temperature. These procedures afforded 83mg of the title compound as a white solid, mp 269-271 °C.

Example 10: (S)-N-[[3-[3-Fluoro-4-(3-methylthio-4H-1,2,4-triazol-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

A suspension of 200mg(0.57mmol) of the compound of Example 9 and 121mg(53μL, 0.85mmol) of methyl iodide in 5mL methanol was treated with 53mg(0.63mmol) of solid sodium bicarbonate. The mixture was stirred at ambient temperature for 23h, and the precipitated solid was collected by filtration, and the filter cake was washed with methanol. The filtrate was concentrated in vacuo to afford a gum which was chromatographed over 25g of 230-400 mesh silica gel, eluting with 5%(v/v) methanol and 0.5%(v/v) ammonium hydroxide in dichloromethane. These procedures afforded a white solid, which was recrystallized from methanol to afford 128mg(61%) of the title compound as awhite solid, mp 188.5-190.5 °C.

Example 11: (S)-N-[[3-[3-Fluoro-4-(4H-1,2,4-triazol-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide:

330mg(0.938mmol) of the mercaptan of Example 9 was added to 0.6mL of 20% nitric acid solution, followed by warming on a steam bath for ca. 1min. After this time, an additional 0.6mL of 20% nitric acid was added, followed by warming on a steam bath for 6-7min, at which point all solids had gone into solution. The mixture was cooled to 0 °C and adjusted to pH9 by addition of ammonium hydroxide solution. The mixture was concentrated in vacuo to afford a brown gummy oil, which was chromatographed over 25g of 230-400mesh silica gel, eluting with 5%(v/v) methanol and 0.5%(v/v) ammonium hydroxide in dichloromethane to afford a solid, which was recrystallized from acetonitrile to afford the title compound, mp 204.5-206 °C.

Example 12: (S)-N-[[3-[3-Fluoro-4-(1H-pyrrol-1-yl-3-carboxaldehyde)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide:

A solution of 2.0g(7.5mmol) of the aniline derivative of Example 9 and 1.68g(10.5mmol) of 2,5-dimethoxy-3-tetrahydrofurancarboxaldehyde in 55mL glacial acetic acid was warmed at reflux for 2h. The solution was cooled and the solvent removed under high vacuum, azeotroping the residue with toluene to remove the last traces of acetic acid. The residue was chromatographed over 300g of 230-400mesh silica gel, eluting with dichloromethane and then with 1-3%(v/v) methanol in dichloromethane. These procedures afforded 2.21g of the title compound as a light yellow amorphous solid. Resolution Mass Spectrum: calcd for $C_{17}H_{16}FN_3O_4$: 345.1125. found: 345.1129.

Example 13: (S)-N-[[3-[3-Fluro-4-(3-hydroxymethyl-1H-pyrrol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide:

A solution of 125mg(0.36mmol) of the previous compound in 4mL methanol and 2mL dichloromethane at 0 °C was treated with 7mg(0.18mmol) of sodium borohydride. The solution was allowed to warm to ambient temperature for 4h, followed by dilution with 30mL dichloromethane and extraction with water. Drying (Na_2SO_4) and concentration in vacuo afforded a white solid, which was recrystallized from ethyl acetate-methanol-hexane. These procedures afforded 106mg(84%) of the title compound as a white solid. High Resolution Mass Spectrum (EI): calcd for $C_{17}H_{18}FN_3O_4$: 347.1281. found: 347.1274.

Example 14: (S)-N-[[3-[3-Fluoro-4-(3-carbomethoxy-1H-pyrrol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide:

A solution of 220mg(0.64mmol) of the compound of Example 12 in10mL of 1:1 acetonitrile-methanol was treated with 164mg(0.64mmol) of sodium cyanide, 1.15g(13.2mmol) of activated manganese dioxide, and 60mg(58μL, 1.0mmol) of glacial acetic acid. The mixture was stirred at ambient temperature for 36h, at which point 550mg(6.32mmol) of activated manganese dioxide and 60mg(58μL, 1.0mmol) of glatial acetic acid were added. The solution was stirred for an additional 24h, and was filtered through celite, washing the filter cake with methanol. The filtrate was concentrated in vacuo, diluted with ethyl acetate and extracted with water (3x). The organic layer was dried (Na_2SO_4) and concentrated in vacuo to afford a pink solid. This material was subjected to radial chromatography on a 2mm chromatotron plate, eluting with dichloromethane and then with 1-2%(v/v) methanol in dichloromethane. These procedures afforded

170mg(71%) of the title compound as a white solid. Analysis: calcd for $C_{18}H_{18}FN_3O_5$: C, 57.60; H, 4.83; N, 11.20. found: C, 57.29; H, 5.19; N, 11.07.

Example 15: (S)-N-[[3-[3-Fluoro-4-(1H-pyrrol-1-yl-3-carboxaldehyde)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide, methoxime:

A solution of 150mg(0.43mmol) of the compound of Example 12 in 5mL of 1:1 methanol-dichloromethane was treated with 44mg(0.52mmol) of methoxylamine hydrochloride and 36mg(0.26mmol) of potassium carbonate, followed by stirring at ambient temperature for 18h. The mixture was diluted with dichloromethane and was extracted with water (3x). Drying(Na_2SO_4) and concentration in vacuo afforded a red-brown-solid. This material was subjected to radial chromatography on a 2mm chromatotron plate, eluting with dichloromethane and then with 1-2%(v/v) methanol in dichloromethane. These procedures afforded 101mg(63%) of the title compound as a white solid which was a mixture of E- and Z- double bond stereoisomers. High Resolution Mass Spectrum (EI): calcd for $C_{18}H_{19}FN_4O_4$: 374.1390. found: 374.1390.

Example 16: (S)-N-[[3-[3-Fluoro-4-(3-(hydroxyiminomethyl)-1H-pyrrol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide:

A solution of 150mg(0.43mmol) of the aldehyde of Example 12 and 36mg(0.26mmol) of potassium carbonate in 10mL of 1:1 methanol-dichloromethane was treated with 36mg(0.52mmol) of hydroxylamine hydrochloride, followed by stirring at ambient temperature for 48h. The mixture was diluted with ethyl acetate, extracted with water (3x), dried (Na_2SO_4) and concentrated in vacuo to afford an off-white solid. This material was subjected to radial chromatography on a 2mm chromatotron plate, eluting with 2-4%(v/v) methanol in dichloromethane. These procedures afforded 90mg(58%) of the title compound as a white solid. ^{1}H NMR (DMSO) δ 11.07, 10.5, 8.24, 8.01, 7.85, 7.70, 7.62, 7.40, 7.30, 7.14, 6.63, 6.48, 4.75, 4.16, 3.77, 3.42, 1.83.

Example 17: (S)-N-[[3-[3-Fluoro-4-(4-acetyl-1H-1,2,3-triazol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide:

(S)-N-[[3-[4-Azido-3-fluorophenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide:

A solution of 4.0g(14.96mmol) of (S)-N-[3-[3-Fluoro-4-aminophenyl]-2-oxo-5-oxazolidinyl]methylacetamide from Example 9 in 40mL of 6N HCl solution at 0 °C was treated portionwise with 4.12g(59.84mmol) of sodium nitrite, followed by

stirring at 0 °C for 2h. The mixture was then treated in several portions with a solution of 1.94g(29.92mmol) of sodium azide and 24.52g(0.30mol) of sodium acetate in in 50mL of water. After addition was complete, solution was extracted with ethyl acetate, and the organic layer was dried (Na_2SO_4) and concentrated in vacuo to afford 4.1g(93%) of the title compound as a light yellow solid, sufficiently pure for further use. ^{1}H NMR ($CDCl_3$) δ 8.22, 7.59, 7.33, 4.72, 4.10, 3.72, 3.40, 1.90.

(S)-N-[[3-[3-Fluoro-4-(4-acetyl-1H-1,2,3-triazol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide:

A solution of 500mg(1.7mmol) of the previous azide in 25ml benzene was treated with 347mg(5.1mmol) of 3-butyn-2-one followed by warming at reflux for 18h. The mixture was cooled and the 407mg(66%) of the title compound was isolated by filtration of the reaction mixture. High Resolution Mass Spectrum (EI): calcd for $C_{16}H_{16}FN_5O_4$: 361.1186. found: 361.1183.

Example 18: (S)-N-[[3-[3-Fluoro-4-(4-(1-hydroxyethyl)-1H-1,2,3-triazol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide:

A solution of 150mg(0.40mmol) of the compound of Example 17 in 10mL 1:1 THF-methanol was treated with 15mg(0.4mmol) of sodium borohydride followed by stirring at ambient temperature for 18h. The mixture was concentrated in vacuo, dissolved in 1:1 methanol-dichloromethane and filtered. The filtrate was concentrated in vacuo and the residue was subjected to radial chromatography on a 2mm chromatotron plate. These procedures afforded 120mg(80%) of the title compound as awhite solid. Mass Spectrum (EI): m/z 363, 291, 276, 232, 217, 207, 191, 179, 163, 148, 135, 123, 85, 56.

Example 19: (S)-N-[[3-[3-Fluoro-4-(4-(1-hydroxyiminomethyl)--1H-1,2,3-triazol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide:

A solution of 150mg(0.40mmol) of the compound of Example 17 in 10mL of 1:1 THF-methanol was treated with 66mg(0.96mmol) of hydroxylamine hydrochloride and 66mg(0.48mmol) of potassium carbonate, followed by stirring at ambient temperature for 8h, and then warming at reflux for 2h. The mixture was concentrated in vacuo, and the residue was subjected to radial chromatography on a 2mm chromatotron plate, eluting with 5%(v/v) methanol in dichloromethane. These procedures afforded 30mg(20%) of the title compound as a white solid. Mass Spectrum (EI): m/z 376, 332, 318, 287, 274, 245, 220, 202, 187, 175, 163, 149, 139, 82, 56.

Example 20: (S)-N-[[3-[3-Fluoro-4-(4-carbomethoxy-1H-1,2,3-triazol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide:

A solution 1.0g(3.4mmol) of the azide of Example 17 in 50mL benzene was treated with 573mg(6.8mmol) of methyl propiolate followed by warming at reflux for 24h. The mixture was cooled and the product isolated by filtration of the reaction mixture. These procedures afforded 880mg of the title compound as a white solid. High Resolution Mass Spectrum (EI): calcd for $C_{16}H_{16}FN_5O_5$: 377.1135. found: 377.1131.

Example 21: (S)-N-[[3-[3-Fluoro-4-(1H-1,2,3-triazol-1-yl-4-carboxaldehyde)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide:

A solution of 1.70g(5.8mmol) of the azide of example 17 in 50mL benzene was treated with 4.46g(34.8mmol) of 1,1-diethoxy-2-propyne followed by warming at reflux for 18h. The solution was treated with 1.0g(7.80mmol) of 1,1-diethoxy-2-propyne followed by warming at reflux for an additional 3h. The solution was cooled and concentrated in vacuo to afford an oil which was chromatographed over 200g of 230-400mesh silica gel, eluting with 2-3%(v/v) methanol in dichloromethane to afford2.0g(80%) of (S)-N-[[3-[3-Fluoro-4-(4-(diethoxymethyl)-1H-1,2,3-triazol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide and (S)-N-[[3-[3-Fluoro-4-(5-(diethoxymethyl)-1H-1,2,3-triazol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide as an inseparable mixture of isomers. Of this material, 410mg(0.973mmol) was dissolved in 10mL THF and treated with 1mL of 1N HCl solution followed by stirring at ambient temperature for 48h, and then warming at reflux for 1h. The mixture was dissolved in ethyl acetate and extracted with water. Drying(Na_2SO_4) and concentration in vacuo afforded an oil which was subjected to radial chromatography on a 2mm chromatotron plate eluting with 7%(v/v) methanol in dichloromethane. The less polar fraction [110mg(33%)] from the chromatography proved to be the title compound, isolated as a white solid. ^1H NMR ($CDCl_3$) δ 8.60, 7.99, 7.85, 7.36, 6.1, 4.86, 4.12, 3.89, 3.72, 2.04.

Example 22: (S)-N-[[3-[3-Fluoro-4-(4-hydroxymethyl-1H-pyrazol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide:

Methyl 3-pyrazolecarboxylate hydrochloride:

10mL of methanol at 0 °C was treated dropwise with 1mL acetyl chloride, followed by addition of 2.0g(17.84mmol) of 4-pyrazolecarboxylic acid, followed by

warming the mixture at reflux for 18h. The solution was cooled and concentrated in vacuo to afford 2.6g(90%) of the title compound as a white solid. ^{1}H NMR (CD_3OD) δ 8.25, 3.86.

4-(4-Carbomethoxy-1H-pyrazol-1-yl)-3-Fluoro-1-nitrobenzene:

A solution of 2.9g(17.84mmol) of the previous compound and 4.93g(35.68mmol) of potassium carbonate in 85mL DMSO was treated with 2.83g(17.84mmol) of 3,4-difluoronitrobenzene. The solution was warmed at 90 °C for 16h, followed by cooling, dilution with chloroform and extraction with water (5x). Drying (Na_2SO_4) and concentration in vacuo afforded 4.17g(88%) of the title compound as an off-white solid. ^{1}H NMR ($CDCl_3$) δ 8.65, 8.28, 8.20, 3.91.

4-(4-Carbomethoxy-1H-pyrazol-1-yl)-3-Fluoro-1-(phenylmethoxycarbonylamino)benzene:

A solution of 4.17g(15.7mmol) of the previous compound in 200mL THF was treated with 1g of W-2 Raney nickel, followed by hydrogenation on a Parr shaker under 45psi hydrogen pressure for 18h. The mixture was filtered through celite, and the filtrate concentrated in vacuo to afford an off-white solid, which was dissolved in 30mL THF and 5mL acetone and treated with 34mL saturated sodium bicarbonate solution, followed by cooling to 0°C and and addition of 3.21g(2.69mL, 18.8mmol) of benzyl chloroformate. The solution was stirred at 0°C for 1h, and then was allowed to warm to ambient temperature for 18h. The mixture was concentrated in vacuo, and the resulting aqueous layer was extracted with ethyl acetate (3x). The organic layer was dried (Na_2SO_4) and concentrated in vacuo to afford 3.1g(53%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 8.41, 8.10, 7.79, 7.64, 7.40, 7.10, 6.88, 5.23, 3.88.

4-(4-hydroxymethyl-1H-pyrazol-1-yl)-3-Fluoro-1-(phenylmethoxycarbonylamino)benzene:

A solution of 3.og(8.13mmol) of the previous compound in 20mL anhydrous THF was treated with 1.42g(65.04mmmol) of lithium borohydride, followed by stirring at ambient temperature for 18h. The solution was treated with 5mL saturated sodium bicarbonate solution, followed by concentration in vacuo. The mixture was diluted with ethyl acetate and extracted with water. Drying (Na_2SO_4) and concentration in vacuo afforded a residue which was chromatographed over 150g of 230-400mesh silica gel, eluting with 2%(v/v) methanol in dichloromethane. These procedures afforded 1.63g(59%) of the title compound as a white solid. High Resolution Mass Spectrum (EI): calcd for $C_{18}H_{16}FN_3O_3$: 341.1176. found: 341.1180.

4-(4-[(tetrahydropyran-2-yl)oxymethyl]-1H-pyrazol-1-yl)-3-Fluoro-1-(phenylmethoxycarbonylamino)benzene:

A solution of 1.63g(4.77mmol) of the previous compound in 30mL dichloromethane was treated with 400mg(4.75mmol) of dihydropyran and 10mg of p-toluenesulfonic acid. The solution was stirred at ambient temperature for 18h, followed by extraction with 30mL saturated sodium bicarbonate solution and water(30mL). Drying (Na_2SO_4) and concentration in vacuo afforded a solid which was chromatographed over 85g of 230-400mesh silica gel eluting with 20%(v/v) ethyl acetate in hexane. These procedures afforded 2.0g(99%) of the title compound as a white solid. High Resolution Mass Spectrum (EI): calcd for $C_{23}H_{24}FN_3O_4$: 425.1751. found: 425.1747.

(R)-[3-[3-Fluoro-4-(4-[(tetrahydropyran-2-yl)oxymethyl]-1H-pyrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methanol:

A solution of 1.43g(3.36mmol) of the previous compound in 10mL THF at -78 ^{o}C was treated with 3.7mL(1.0M, 3.7mmol) of lithium bis(trimethylsilyl)amide in THF, followed by stirring at 78 ^{o}C for 30min. The solution was then treated with 533mg(0.52mL, 3.7mmol) of (R)-(-)-glycidyl butyrate followed by stirring at 78 ^{o}C for 30min, warming to 0 ^{o}C for 30min, and then gradual warming to ambient temperature for 18h. The solution was treated with 1mL saturated ammonium chloride solution and diluted with ethyl acetate. The mixture was extracted with with water, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over 70g of 230-400mesh silica gel, eluting with 2%(v/v) methanol in dichloromethane. These procedures afforded 910mg(70%) of the title compound as a white solid. High resolution Mass Spectrum (EI): calcd for $C_{19}H_{22}FN_3O_5$: 391.1543. found: 391.1542.

(R)-[3-[3-Fluoro-4-(4-[(tetrahydropyran-2-yl)oxymethyl]-1H-pyrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methanesulfonyloxymethane:

A solution 0.820mg(2.1mmol) of the previous compound and 318mg(3.15mmol) triethylamine in 25mL of dichloromethane at 0 ^{o}C was treated with 360mg(2.62mmol) of methanesulfonyl chloride. The solution was stirred at 0 ^{o}C for 1h. The solution was diluted with dichloromethane and extracted with water. Drying (Na_2SO_4) and concentration in vacuo afforded 986mg(99%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.95, 7.92, 7.74, 7.25, 4.97, 4.75, 4.50, 4.20, 4.01, 3.93, 3.59, 3.12, 1.85, 1.74, 1.56.

(R)-[3-[3-Fluoro-4-(4-[(tetrahydropyran-2-yl)oxymethyl]-1H-pyrazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl azide:

A solution of 986mg(2.1mmol) of the previous compound and 683mg(10.5mmol) of sodium azide in 20mL DMF was warmed at 60 °C for 18h, followed by dilution with ethyl acetate and extraction with water. Drying (Na_2SO_4) and concentration in vacuo afforded 874mg(99%) of the title compound as a white solid. ^1H NMR ($CDCl_3$) δ 7.98, 7.87, 7.74, 7.23, 4.82, 4.72, 4.50, 4.11, 3.90, 3.73, 3.61, 3.55, 1.81, 1.73, 1.58.

(S)-N-[[3-[3-Fluoro-4-(4-[(tetrahydropyran-2-yl)oxymethyl]-1H-pyrazol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide:

A solution of 874mg(2.1mmol) of the previous compound in 15mL ethyl acetate was treated 200mg of 10% palladium on carbon, followed by hydrogenation at one atmosphere for 1.5h. The solution was filtered through celite and the filtrate concentrated in vacuo to afford a brown solid, which was dissolved in 3mL pyridine and treated with 428mg(4.2mmol) of acetic anhydride, followed by stirring at ambient temperature for 18h. The solution was diluted with ethyl acetate and extracted with water. Drying (Na_2SO_4) and concentration in vacuo afforded a solid which was chromatographed over 50g of 230-400 mesh silica gel eluting with 1-2%(v/v) methanol in dichloromethane. These procedures afforded 626mg(69%) of the title compound as a white solid. High Resolution Mass Spectrum (EI): calcd for $C_{21}H_{25}FN_4O_5$: 432.1809. found: 432.1811.

(S)-N-[[3-[3-Fluoro-4-(4-hydroxymethyl-1H-pyrazol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide:

A solution of 300mg(0.693mmol) of the previous compound in 15mL methanol was treated with 40mg of p-toluenesulfonic acid, followed by stirring at ambient temperature for 18h. The mixture was concentrated in vacuo and the residue dissolved in ethyl acetate and extracted with saturated sodium bicarbonate solution and water. Drying (Na_2SO_4) and concentration in vacuo afforded 140mg(58%) of the title compound as a white solid. High Resolution Mass Spectrum (EI): calcd for $C_{16}H_{17}FN_4O_4$: 349.1312. found: 349.1321.

Example 23: (S)-N-[[3-[3-Fluoro-4-[3-(2-carboethoxyvinyl)-1H-pyrrol-1-yl]phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide:

A solution of 805mg(3.19mmol) of diisopropyl ethoxycarbonylmethylphosphonate in 7mL THF at 0 °C was treated with 3.19mL(1.0M, 3.19mmol) of potassium tert-butoxide in THF solution, followed by warming to ambient temperature for 1h. The solution was cooled to -78°C and treated via cannula with a solution of 500mg(1.45mmol) of the compound of Example

12 in 4mL THF. The solution was stirred at -78 °C for 30min, followed by warming to ambient temperature for 2h. The solution was quenched by addition of 1mL saturated ammonium chloride solution followed by dilution with ethyl acetate and extraction with water. Drying (Na_2SO_4) and concentration in vacuo afforded a yellow solid, which was chromatographed over 100g of 230-400mesh silica gel, eluting with 1-2%(v/v) methanol in dichloromethane. These procedures afforded 497mg(83%) of the title compound as a light yellow solid. ^{1}H NMR ($CDCl_3$) δ 7.65, 7.37, 7.27, 7.20, 6.97, 6.56, 6.17, 6.02, 4.82, 4.24, 4.08, 3.83, 3.70, 2.04, 1.33.

Example 24: (S)-N-[[3-[3-Fluoro-4-[3-(2-carboethoxyethyl)-1H-pyrrol-1-yl]phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide:

A soluiton of 150mg(0.36mmol) of the compound of Example 23 and 54mg(0.54mmol) of copper [I] chloride in 15mL 1:1 Methanol-THF at 0 °C was treated with 136mg(3.6mmol) of sodium borohydride. The solution was stirred at 0 °C for 30min and then warmed to ambient temperature for 1h. The solution was treated with 2mL saturated ammonium chloride solution, followed by filtration through celite. The filtrate was concentrated in vacuo and the residue was diluted with ethyl acetate and extracted with water (3x). Drying (Na_2SO_4) and concentration in vacuo afforded 150mg(99%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.60, 7.34, 7.33, 6.91, 6.81, 6.21, 5.97, 4.81, 4.15, 4.08, 3.82, 3.72, 3.65, 2.87, 2.62, 2.04, 1.26.

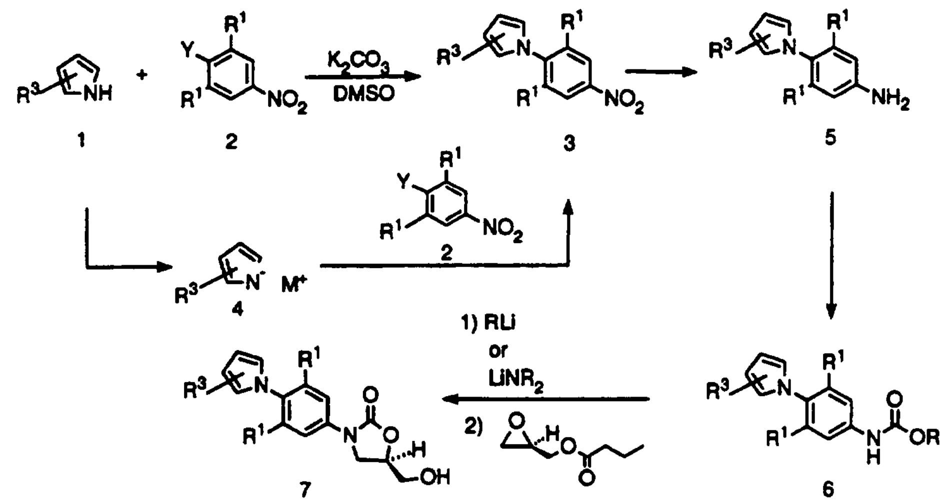
Example 25: (S)-N-[[3-[3-Fluoro-4-[3-(3-hydroxypropyl)-1H-pyrrol-1-yl]phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide:

A solution of 275mg(0.66mmol) of the compound of Example 24 in 15mL THF was treated with 287mg(13.2mmol) of lithium borohydride followed by stirring at ambient temperature for 18h. The solution was treated with 1mL of saturated ammonium chloride solution, diluted with ethyl acetate, and extracted with water (3x). Drying (Na_2SO_4) and concentration in vacuo afforded an oil, which was chromatographed over 20g of 230-400mesh silica gel eluting with 2-4%(v/v) methanol in dichloromethane. These procedures afforded 96mg(39%) of the title compound as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.74, 7.66, 7.38, 7.27, 7.18, 6.95, 6.61, 5.98, 4.82, 4.37, 4.27, 4.09, 3.83, 3.68, 2.88, 2.82, 2.62, 2.04, 1.79.

Example 26: (S)-N-[[3-[3-Fluoro-4-[3-(3-methanesulfonylaminopropyl)-1H-pyrrol-1-yl]phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide:

A solution of 100mg(0.266mmol) of the comound of Example 25 (previously dried at 60 °C under 0.1mmHg for 18h prior to use) and 88mg(120μL, 0.88mmol) of triethylamine in 2mL dichloromethane at 0 °C was treated with 85mg(58μL, 0.73mmol) of methanesulfonyl chloride, followed by stirring at 0 °C for 30min. The solution was diluted with dichloromethane and extracted with water (2x) and saturated sodium bicarbonate solution. Drying (Na_2SO_4) and concentration in vacuo afforded a solid which was dissolved in 2mL DMF and treated via cannula to a 0 °C solution of 38mg(0.40mmol) of methanesulfonamide in 2mL DMF which had been previously treated with 10mg(17mg of 60% in oil, 0.43mmol) of sodium hydride. The solution was then warmed at 60 °C for 18h. The solution was cooled and the DMF removed in vacuo, and the residue was dissolved in ethyl acetate and extracted with water (2x). Drying (Na_2SO_4) and concentration in vacuo afforded a solid which was subjected to radial chromatography on a 2mm chromatotron plate, eluting with 1-4%(v/v) methanol in dichloromethane. These procedures afforded 31mg(26%) of the title compound as a white solid. ^1H NMR ($CDCl_3$) δ 7.61, 7.56, 7.35, 7.23, 6.92, 6.81, 6.19, 6.06, 4.81, 4.29, 4.07, 3.82, 3.67, 3.22, 2.95, 2.62, 2.04, 1.90.

CHART I



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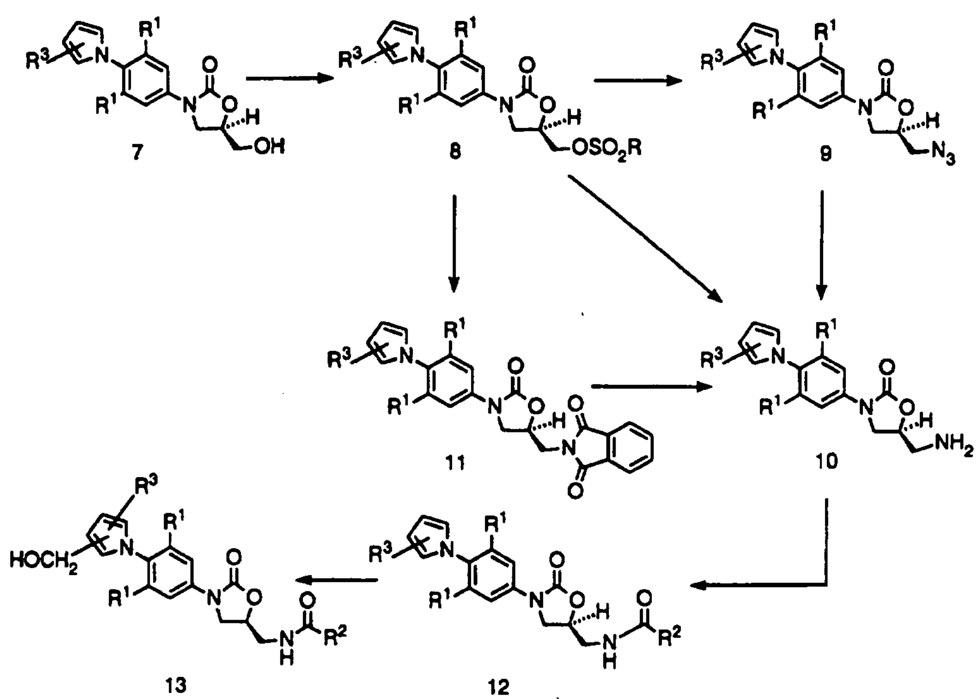

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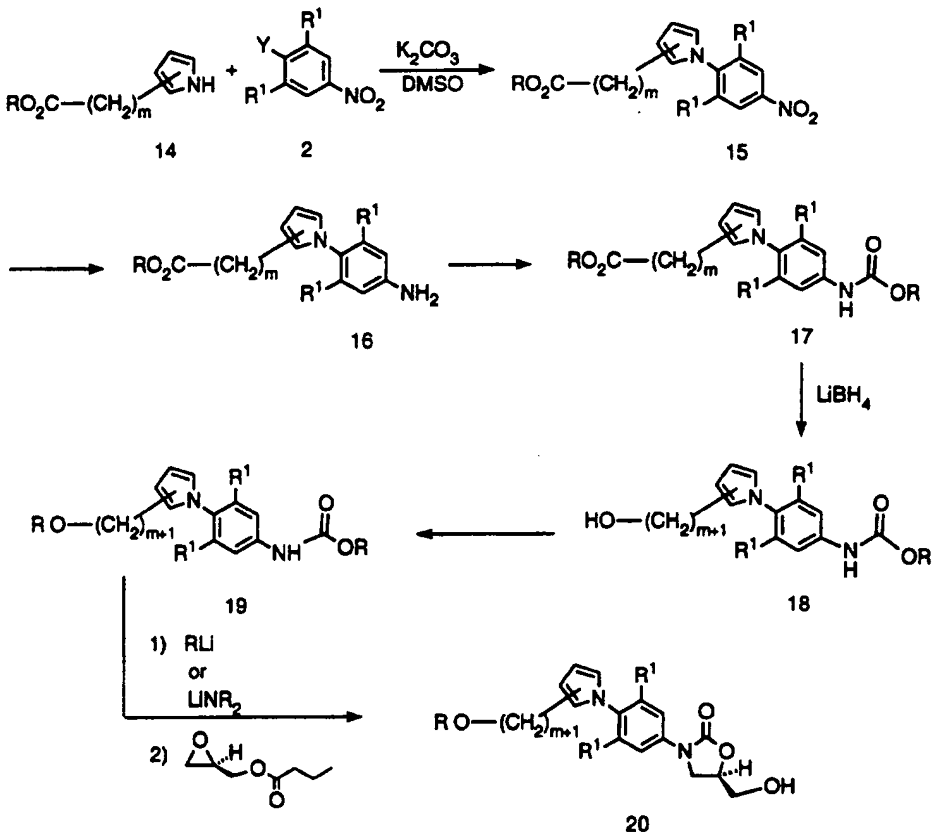

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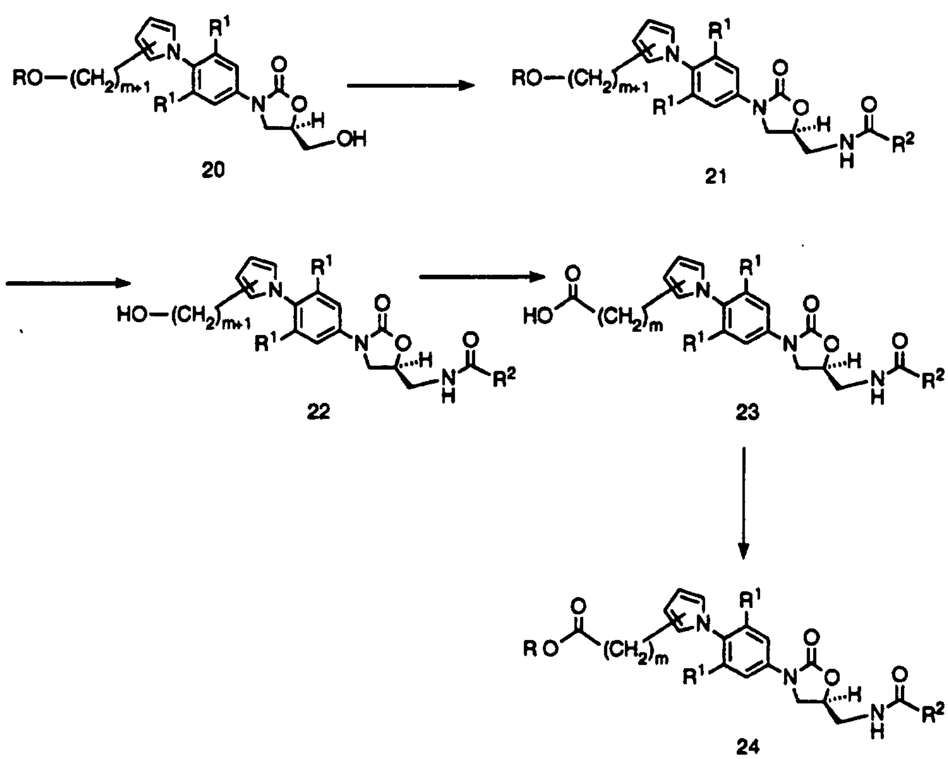

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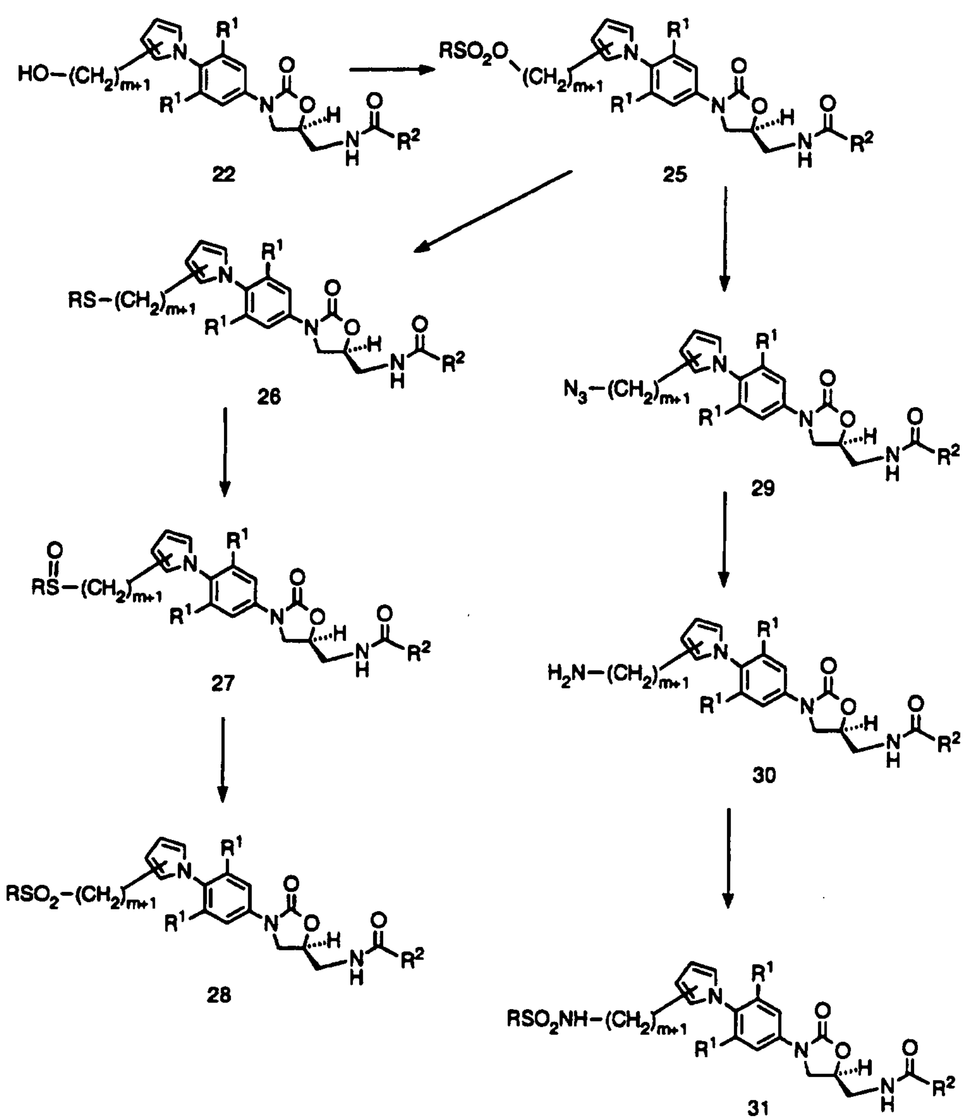
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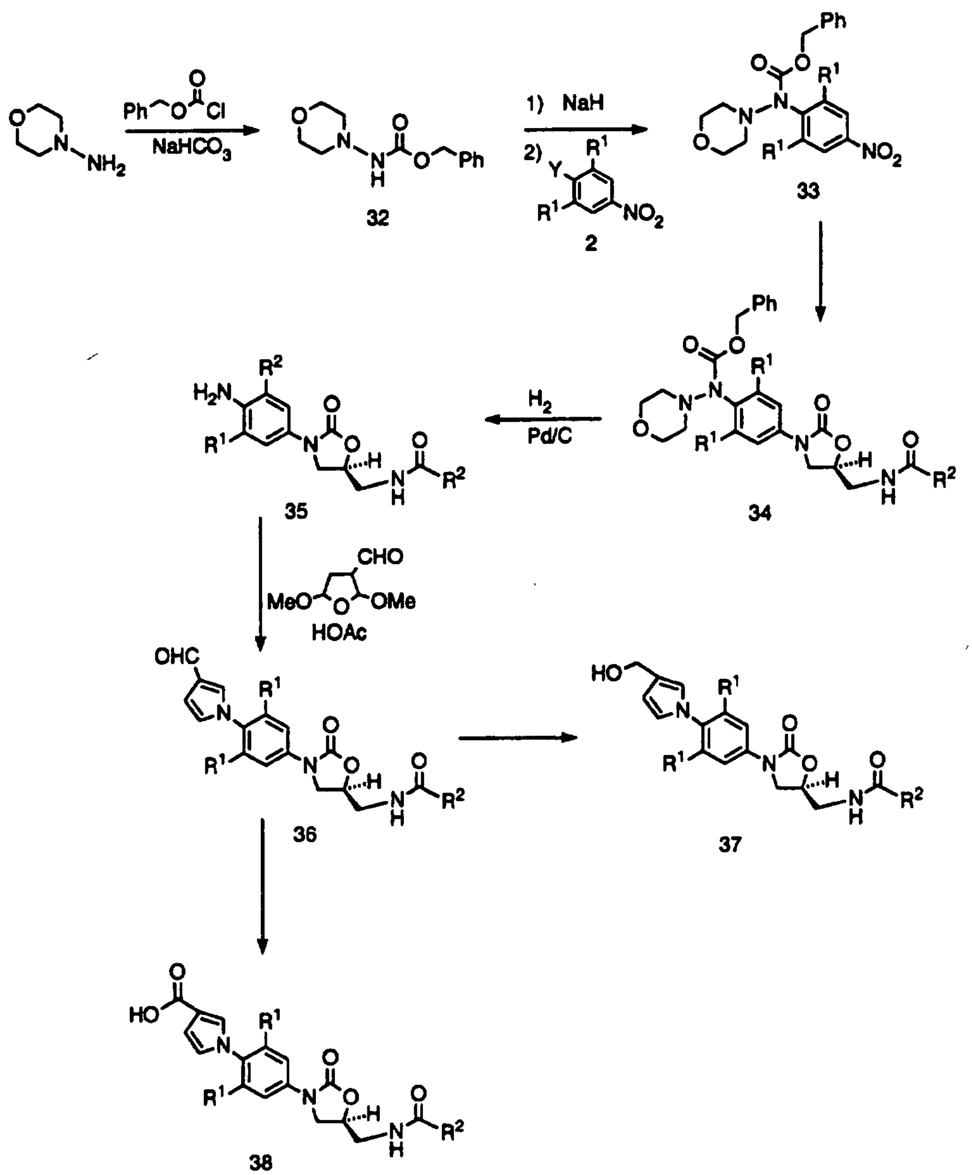
CHART VI



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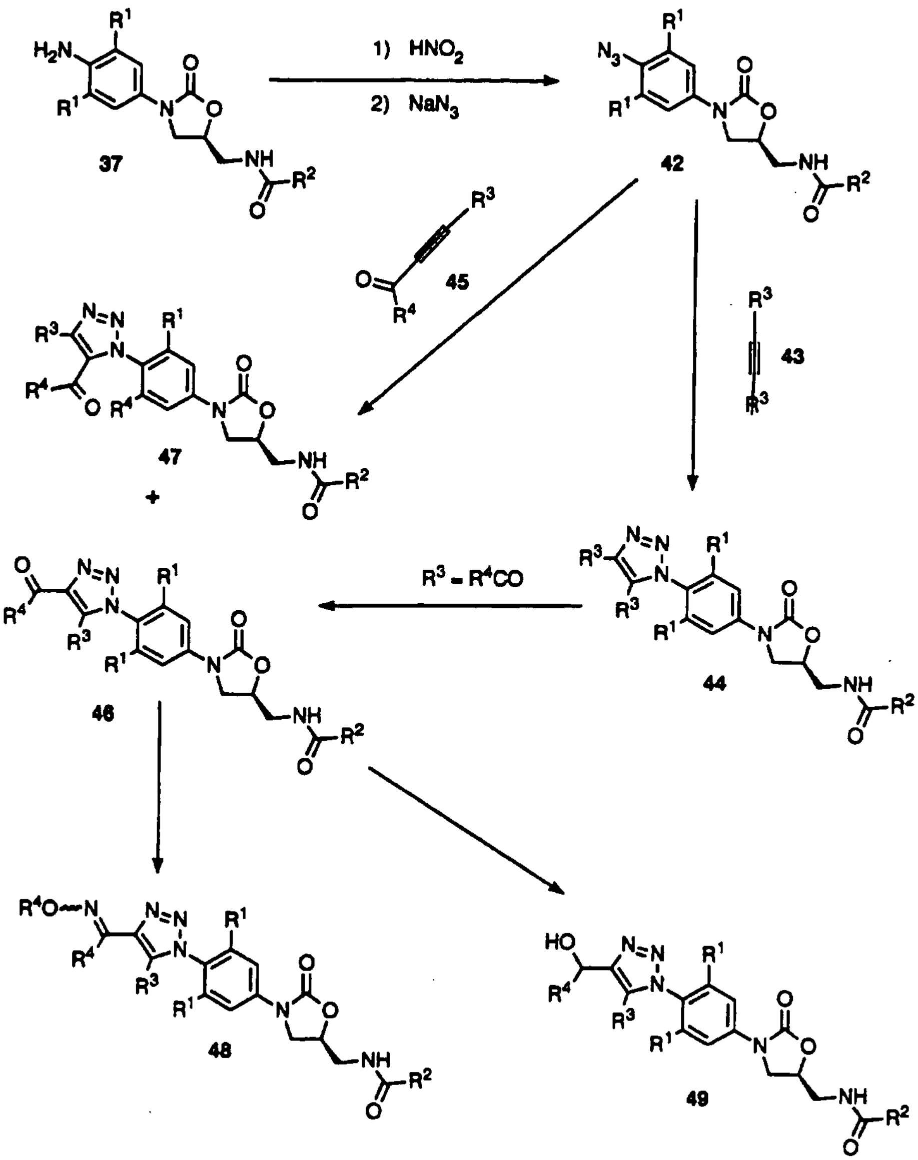

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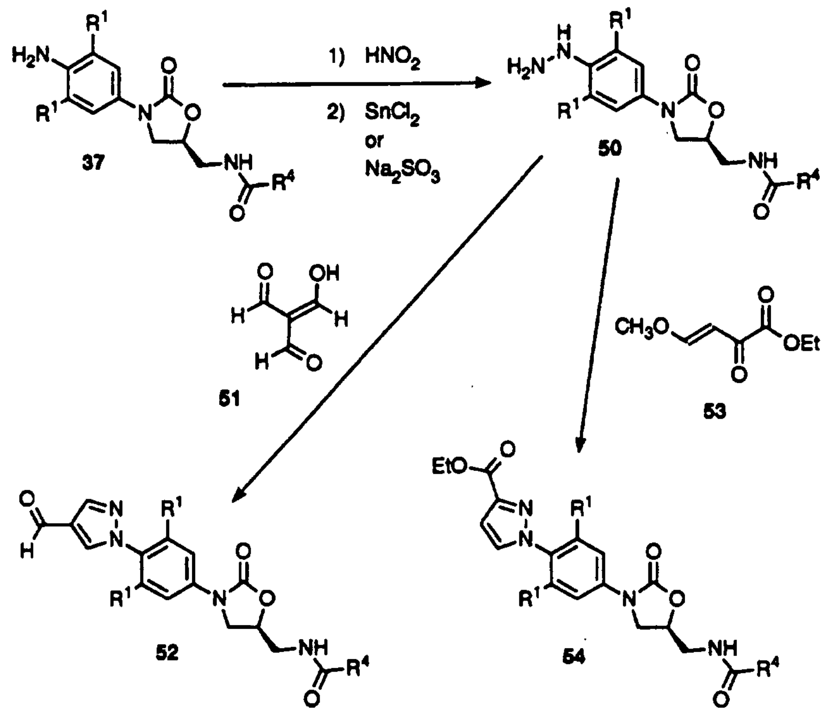
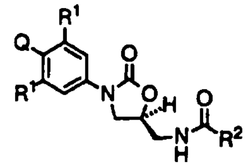


WHAT IS CLAIMED:

1. A compound structurally represented by Formula I

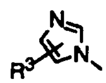


or pharmaceutically acceptable salts thereof wherein:

Q is a hetero-aromatic 5-member ring bound to the aromatic ring of I at the nitrogen of the structures i, ii, iii, iv, v, vi, vii, viii, or ix:


i


ii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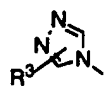
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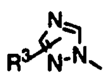
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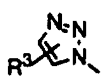
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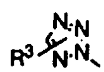
vii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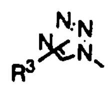
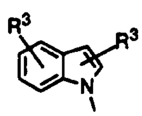

ix

or alternatively Q can be a benzoannulated hetero-aromatic 5-member ring bound to the aromatic ring of I at the nitrogen of the structures x, xi, xii, xiii, xiv, xv, xvi or xviii: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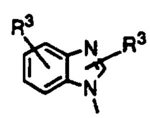
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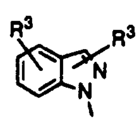
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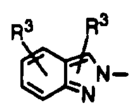
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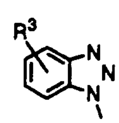
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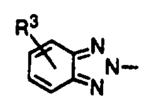
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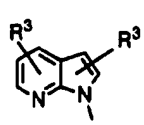
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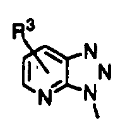
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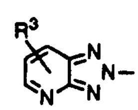
xviii

R^1 is independentlyl H, OCH_3, F, or Cl;

R^2 is (a) hydrogen,

(b) C_1-C_8 alkyl optionally substituted with one or more of the following: F, Cl, hydroxy, C_1-C_8 alkoxy, C_1-C_8 acyloxy;

(c) C_3-C_6 cycloalkyl;

(d) amino;

(e) C_1-C_8 alkylamino;

(f) C_1-C_8 dialkylamino;

(g) C_1-C_8 alkoxy;

R^3 is each independently selected from

(a) H,

(b) F, Cl, Br,

(c) OR^4,

(d) SR^4,

(e) $S(O)_nR^4$ (n is 1 or 2),

(f) CN,

(g) O_2CR^4,

(h) $NHCOR^4$,

(i) $NHCO_2R^4$,

(j) $NHSO_2R^4$,

(k) CO_2R^4,

(l) $CON(R^4)_2$,

(m) COR^4,

(n) C_1-C_8 straight or branched chain alkyl or C_3-C_8 cycloalkyl, optionally substituted with one or more of (a)-(m), or

(o) Phenyl, optionally substituted with one or more of the preceeding groups listed under (a)-(n); and

R^4 is (a) H,

(b) C_1-C_6 straight or branched chain alkyl or C_3-C_8 cycloalkyl, optionally substituted with one or more of fluorine, chlorine, hydroxy, C_1-C_4 alkoxy, C_1-C_4 acyl, C_1-C_4 acyloxy, or $O_2CCH_2N(CH_3)_2$, or

(c) Phenyl, optionally substituted with one or more of fluorine, chlorine, C_1-C_4 straight or branched chain alkyl, hydroxy, C_1-C_4 alkoxy, C_1-C_4 acyl, C_1-C_4 acyloxy, or $O_2CCH_2N(CH_3)_2$.

2. The compound of Claim 1 wherein Q is i, ii, iii or v.

3. The compound of Claim 1 wherein Q is x.

4. The compound of Claim 1 wherein R^1 is independently hydrogen or F.

5. The compound of Claim 4 wherein at least one R^1 is F.

6. The compound of Claim 1 wherein R^2 is methyl, dichloromethyl, methoxy, or hydrogen.

7. The compound of Claim 1 wherein R^3 is hydrogen, C_1-C_8alkylhydroxy, C_1-C_8 alkyl or C_1-C_4alkoxycarbonyl.

8. The compound of Claim 1 which is

a) (S)-N-[[3-[3-Fluoro-4-(1H-imidazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

b) (S)-N-[[3-[3-Fluoro-4-(1H-1,2,4-triazol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide;

c) (S)-N-[[3-[3-Fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide;

d) (S)-N-[[3-[3-Fluoro-4-(1H-1,2,3-triazol-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-2,2-dichloroacetamide;

e) (S)-N-[[3-[3-Fluoro-4-(1H-pyrrol-1-yl-3-carboxaldehyde)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide, methoxime;

f) (S)-N-[[3-[3-Fluoro-4-(3-(hydroxyiminomethyl)-1H-pyrrol-1-yl)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide;

g) (S)-N-[[3-[3-Fluoro-4-(1H-1,2,3-triazol-1-yl-4-carboxaldehyde)phenyl]-2-oxo-5-oxazoldinyl]methyl]acetamide;

h) (S)-N-[[3-[3-Fluoro-4-(4-(1-hydroxyiminoethyl)-1H-1,2,3-triazole-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide; or

i) (S)-N-[[3-[3-Fluoro-4-(4-(1-methoxyiminoethyl)-1H-1,2,3-triazole-1-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide.

9. The use of a compound of Formula I as set forth in Claim 1 to prepare a medicament useful for treating antimicrobial infections in patients suffering therefrom comprising administering an antibacterially effective amount of a

compound of Formula I.

10. The use of Claim 9 wherein the antibacterially effective amount is from about 0.1 to about 100 mg/kg of body weight/day.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/00718

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D413/10 A61K31/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 352 781 (DU PONT DE NEMOURS) 31 January 1990 cited in the application see claims ---	1,9,10
A	WO,A,93 09103 (UPJOHN CO) 13 May 1993 cited in the application see claims ---	1,9,10
P,A	WO,A,95 07271 (UPJOHN CO) 16 March 1995 see claims -----	1,9,10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
3 June 1996	13.06.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 96/00718

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0352781	31-01-90	US-A-	4948801	14-08-90
		AU-B-	622465	09-04-92
		AU-B-	3911589	01-02-90
		CA-A-	1337526	07-11-95
		JP-A-	2124877	14-05-90
		US-A-	5130316	14-07-92
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		EP-A-	0610265	17-08-94
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		CA-A-	2168560	16-03-95